NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Use and Safety of Paxlovid During Pregnancy
Protocol number	C4671037
Protocol version identifier	Protocol V2.0
Date	10 November 2022
EU Post-Authorisation Study (PAS) register number	Study will be registered before start of data collection
Active substance	Combination of the oral protease inhibitors nirmatrelvir and ritonavir (ATC code J05AE30)
Medicinal product	Paxlovid
Product reference	PF-07321332/ritonavir
Procedure number	Conditional marketing authorisation EMEA/H/C/005973/0000
Marketing Authorisation Holder(s) (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No
Research question and objectives	The research question is: what are the prevalence and comparative safety of adverse pregnancy, offspring, and maternal outcomes in women exposed to Paxlovid during pregnancy? The primary study objective is to estimate the birth prevalence, prevalence ratio, and prevalence difference of the following adverse pregnancy, offspring, and maternal outcomes in women who are exposed to Paxlovid during

	pregnancy compared with those in women who are exposed to molnupiravir, where available, during pregnancy or to neither Paxlovid nor molnupiravir during pregnancy: Pregnancy outcomes • Spontaneous abortion • Elective termination • Stillbirth • Preterm delivery Offspring outcomes • Major congenital malformations • Intrauterine growth retardation/small for gestational age Maternal outcomes • Gestational diabetes • Postpartum haemorrhage • Maternal death
Country(-ies) of study	• France • Spain • United Kingdom • Other countries in Europe are under evaluation
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Marketing Authorisation Holder

Marketing Authorisation Holder	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AEMPS	Spanish Medicines Agency of Medicines and Medical Devices [Agencia Española de Medicamentos y Productos Sanitarios]
AIFA	Italian Medicines Agency [Agenzia Italiana del Farmaco]
ALD	List of chronic conditions registered in France [Affections de Longue Durée]
ARS Toscana	Regional Health Agency of Tuscany, Italy [Agenzia Regionale di Sanità della Toscana]
ASSIR registers	Sexual and reproductive healthcare registers (Spain)
ATC	Anatomical Therapeutic Chemical (classification system)
BIFAP	Base de Datos para la Investigación Farmacoepidemiológica en Atención Primària (Spain)
BPE	Bordeaux PharmacoEpi, Université de Bordeaux (France)
CDM	Common data model
CESREES	Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé (France)
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CMA	Conditional marketing authorisation
CMUc	*Couverture médicale universelle complémentaire* indicator of low-income status (France)
CNAM	Caisse Nationale de l'Assurance Maladie (France)
CNIL	French Data Protection Commission [Commission Nationale de l'Informatique et des Libertés]

Abbreviation	Definition
COVID-19	Coronavirus disease 2019
CPRD	Clinical Practice Research Datalink (UK)
CPRD GOLD	General Practitioner Online Database (of CPRD)
DAP	Data access partner
DCIR	Individual outpatient healthcare data [Datamart de Consommation Inter Régime] (France)
DRE	Digital Research Environment
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPhMRA	European Pharmaceutical Market Research Association
ETL	Extraction, transformation, and loading
EU	European Union
EU PAS Register	European Union Electronic Register of Post-authorisation Studies
EUROCAT	European network of population-based registries for the epidemiological surveillance of congenital anomalies
FAIR	Findability, Accessibility, Interoperability, and Re-use of digital assets
GPP	Good Pharmacoepidemiology Practices
GVP	Guideline on Good Pharmacovigilance Practices
HES	Hospital Episode Statistics
HIV	Human Immunodeficiency Virus
ICD-10	*International Statistical Classification of Diseases, Tenth Revision*
ICD-9	*International Statistical Classification of Diseases, Ninth Revision*

Abbreviation	Definition
ICPC	International Classification of Primary Care
ICPE	International Conference on Pharmacoepidemiology & Therapeutic Risk Management
IDIAP Jordi Gol or IDIAP	Foundation University Institute for Primary Health Care Research Jordi Gol i Gurina (Spain)
IEC	Independent ethics committee
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
IT	Information technology
KM	Kaplan-Meier
LMP	First day of the last menstrual period
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
NHS	National Health Service
NI	Non-interventional
ONS	Office for National Statistics
PASS	Post-authorisation safety study
PASS-DUS	Drug utilisation study component of the PASS
PASS-safety	Safety component of the PASS
PMSI	National hospital discharge summaries database system (France)
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
RT-PCR	Reverse transcription polymerase chain reaction

Abbreviation	Definition
RTI-HS	RTI Health Solutions, a division of RTI International, a not-for-profit research organisation
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SI-DEP	National Population Screening Information System (France)
SIDIAP	Information System for Research in Primary Care [Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària] Catalonia, Spain
SmPC	Summary of product characteristics
SNDS	French Administrative Healthcare Database [Système National Des Données de Santé] (France)
SNOMED CT	Systematized Nomenclature of Medicine–Clinical Terms
UCD	Common dispensing unit (France)
UK	United Kingdom
US	United States
VAC4EU	Vaccine Monitoring Collaboration for Europe

3. RESPONSIBLE PARTIES

The Marketing Authorisation Holder (MAH) of Paxlovid is Pfizer.

RTI Health Solutions (RTI-HS), University Medical Center Utrecht, Aarhus University, and ARS Toscana, which are members of the SIGMA[1] and VAC4EU[2] consortia, are under contract with Pfizer to develop the post-authorisation safety study (PASS) programme protocol and conduct feasibility checks for the present study. Additional research partner members and collaborators are being included in the study as the country-specific reimbursement, launch timelines, and sales forecasts for Paxlovid become available.

Principal Investigator(s) of the Protocol

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a. Prof. Ehrenstein contributed to earlier versions of the protocol.

Country Coordinating Investigators

The list of study sites and research teams with access to data (data access partners [DAPs]) has been developed as information about the healthcare settings where Paxlovid is distributed, prescribed, and dispensed to patients in specific European countries has become available. Research partners with protocol-based access to data sources are listed below. They have reviewed and provided comments to this protocol and have confirmed interest in participating in this PASS.

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4. ABSTRACT

Title

Use and Safety of Paxlovid During Pregnancy

- Protocol version 2.0, 10 November 2022
- Main author: Andrea Margulis, RTI Health Solutions, on behalf of the SIGMA Paxlovid Research Team

Rationale and background

Paxlovid consists of nirmatrelvir (formerly PF-07321332), a potent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) protease inhibitor, co-administered with a low dose of ritonavir, which acts as a pharmacokinetic enhancer, orally twice a day for 5 days. Paxlovid is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.

The safety of Paxlovid in pregnant women and in individuals with hepatic or renal impairment is not known. The studies on the safety of Paxlovid in pregnant women and in individuals with moderate or severe hepatic or renal impairment are regulatory commitments to the European Medicines Agency (EMA). The safety of Paxlovid in pregnant women is also a regulatory commitment to the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA).

This protocol describes a PASS to assess the safety of Paxlovid in pregnant women in European countries with data sources that have the ability to capture exposure and where the target populations, outcomes, and key covariates can be ascertained.

Research question and objectives

The primary study objective is to estimate the birth prevalence, prevalence ratio, and prevalence difference of the following adverse pregnancy, offspring, and maternal outcomes in women who are exposed to Paxlovid during pregnancy compared with those in women who are exposed to molnupiravir, where available, during pregnancy or to neither Paxlovid nor molnupiravir during pregnancy:

Pregnancy outcomes

- Spontaneous abortion
- Elective termination
- Stillbirth

- Preterm delivery

Offspring outcomes

- Major congenital malformations
- Intrauterine growth retardation/small for gestational age

Maternal outcomes

- Gestational diabetes
- Postpartum haemorrhage
- Maternal death

Study design

The study will focus on pregnant women. Within this population, there will be a descriptive analysis and comparative analyses. Molnupiravir, an antiviral with a similar recommended usage, will be used as an active comparator in the data sources in which it is available; other drugs may be incorporated as active comparators as more information becomes available. At the time of preparing this protocol, molnupiravir was not utilised or its use was not captured by some of the data sources (eg, France and Information System for Research in Primary Care [SIDIAP] in Catalonia, Spain). Therefore, a second comparator group is included in the study: individuals who were at increased risk for progression to severe COVID-19 but had not received Paxlovid or molnupiravir.

This PASS will make secondary use of several data sources from electronic health records and/or claims data in European countries that have the ability to capture Paxlovid exposure and where the target populations, study outcomes, and key covariates can be ascertained. The study period will start on 01 January 2022 (in alignment with regulatory authorisation and launch in Europe) and end as late as possible, with latest data extraction estimated for quarter 1 2025.

Reports to the EMA will include a progress report with a description of project start-up and subsequent activities, a description of the evolution of aspects that have been identified as key challenges for this study, and the list of data sources (per an ongoing feasibility assessment of Paxlovid distribution channels in various countries); 2 annual interim reports with the results of a feasibility assessment that will include the number of Paxlovid-exposed individuals overall and in each target study population, selected characteristics of each exposure group, and preliminary outcome counts; a final report; and, if applicable, a paediatric report 6 months after the end of data collection for the final report.

Population

The target study population will be individuals with COVID-19 who were at increased risk for progression to severe COVID-19, who used Paxlovid or comparator drug molnupiravir, or had not received Paxlovid or molnupiravir (the *unexposed comparison group*), while they are pregnant. Follow-up will start at the time of treatment or eligibility for the unexposed comparison group and for pregnant individuals will end at the earliest of death, disenrollment/migration, end of data availability, or 6 months after the end of pregnancy; for offspring outcomes, offspring follow-up will continue through the earliest of death, disenrollment/migration, end of data availability, or 1 year of age; follow-up for each outcome will end at the occurrence of the given outcome.

Variables

The exposures will be Paxlovid and the comparator molnupiravir, both of which will be ascertained from prescription and pharmacy information or from other data banks (eg, a central COVID-19 therapy distribution registry, if Paxlovid distribution is documented in this manner). See details in the Data sources subsection.

Outcomes will be ascertained from each of the data sources based on algorithms that include diagnosis codes, medication use, procedure codes, information recorded in birth registries, and others. Planned outcomes are as follows:

- Pregnancy outcomes:
  - Spontaneous abortion
  - Elective termination
  - Stillbirth
  - Preterm delivery
- Offspring outcomes
  - Major congenital malformations
  - Intrauterine growth retardation/small for gestational age
- Maternal outcomes
  - Gestational diabetes
  - Postpartum haemorrhage
  - Maternal death

Key variables will include demographics, COVID-19 tests and diagnoses, comorbidities, comedications, COVID-19 vaccination status (as available) and health services utilisation ascertained from all the data banks linked in the selected data sources, including administrative data, coded entries, vaccination registries, birth registries, and others.

Data sources

As of 20 September 2022, the MAH has confirmed that Paxlovid has been supplied to France, Germany, Italy, Spain, Slovenia, Sweden, and the UK, initially or continuing under special government contracts, resulting in different distribution and reimbursement channels being used and subsequent challenges capturing its prescription and distribution. Current information is that prescribed/dispensed Paxlovid should be captured in existing electronic population data sources in France, Spain, and the UK. The Italian Medicines Agency (AIFA) established a national registry for Paxlovid and other antivirals to treat COVID-19. Capture of Paxlovid dispensing/prescriptions in the existing electronic data sources commonly used for pharmacoepidemiological research in Italy at this moment is expected to be minimal. As long as the German government continues to cover payments for Paxlovid, it is expected that Paxlovid prescriptions will not appear in the German Statutory Health Insurance data sources.

The proposed data sources are the French Administrative Healthcare Database (SNDS), SIDIAP (Catalonia, Spain), and Clinical Practice Research Datalink–Aurum (CPRD Aurum) (UK).

The UK OpenSAFELY data source is proposed for exploration as a supplementary data source. The AIFA patient registry is proposed for exploration as a source for the feasibility component in Italy.

The MAH will share additional information about Paxlovid supply and forecast for other European countries as it becomes available, and the research team will evaluate whether Paxlovid use is captured in the electronic data sources that allow longitudinal studies in these countries.

Study size

In this study, the duration of the observation period is bound by the dates for producing regulatory reports. All individuals meeting eligibility criteria during the study observation period will be included. As the summaries of product characteristics (SmPCs) recommend against use in pregnancy, Paxlovid exposure in this population is anticipated to be small.

Data analysis

The study will have a cohort design. Focusing on the target populations, the descriptive component will include tabulations of age, sex, comorbidities, selected concurrent medications, COVID-19 vaccination status, history of COVID-19, current COVID-19 status and setting of Paxlovid use (among Paxlovid users). Comparative analyses will be based on

the estimation of risk/prevalence, risk/prevalence ratios, and risk/prevalence differences. Comparative analyses will control for measured confounding within each data source. Aggregated results from each data source will be combined using meta-analytic techniques as numbers allow. If a study population is too small, analyses will be only descriptive; pooling of results from various data sources will be undertaken only if at least 3 independent data points are available.

Milestones

- Protocol C4671037 V1.0 submission: 31 May 2022 (including pregnant population, population with moderate or severe hepatic impairment and population with moderate or severe renal impairment in a single document)
- Protocol C4671037 V2.0 submission: November 2022 (planned; pregnant population)
- Progress report submission: November 2022 (planned)
- Regulatory protocol endorsement anticipated: quarter 1 or quarter 2 of 2023
- Interim report 1: 12 months after protocol endorsement; interim report 1 estimated for quarter 2 2024[*]
- Interim report 2: 24 months after protocol endorsement; interim report 2 estimated for quarter 2 2025[*]
- Paediatric report (as applicable if Paxlovid is used by pregnant individuals younger than 18 years old[3]): 6 months after the end of data collection for the final report[*]
- Final report: final report estimated for 28 November 2025[*]

[*] Protocol endorsement from EMA is expected in quarter 1 or quarter 2, 2023. Milestones will be updated once protocol endorsement date is known.

5. AMENDMENTS AND UPDATES

Key changes after submission to the EMA-PRAC of protocol C4671037, titled *Use and safety of Paxlovid during pregnancy and among patients with moderate or severe hepatic or renal impairment* (V1.0, dated 31 May 2022), are listed below. Minor (eg, wording) changes are not listed.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	10 November 2022	All protocol	Protocol version 1.0 included 3 populations: pregnant women, individuals with moderate or severe hepatic impairment, and individuals with moderate or severe renal impairment. The protocol was divided into 2: one including the population of pregnant women (the present protocol C4671037), and one including the populations of individuals with moderate or severe hepatic impairment and individuals with moderate or severe renal impairment (protocol C4671047).	Committee for Medicinal Products for Human Use (CHMP) Outcome of procedure EMEA/H/C/005973/MEA/009 received on 15 September 2022
		Cover page 4 8 9 Throughout	The objective related to drug utilisation was removed. This component included a description of women of childbearing age, which was removed per request of the Agency. As a consequence, the description of the population that would be involved in that analysis and the analyses were removed; the labels "PASS-DUS" and "PASS-safety," no longer needed, were removed.	Addressing comment 6 in Final Assessment Report for non-imposed non-interventional PASS protocol - Post-Authorisation Measure 009; EMEA/H/C/005973/MEA/009, dated 15 September 2022 (hereafter in this table, CHMP/PRAC Final Assessment Report)
		Cover page 4 8 9.3	Maternal outcomes are now specified in the objectives: postpartum haemorrhage, gestational diabetes, and maternal death. Other outcomes are now also listed.	Addressing comment 19 in CHMP/PRAC Final Assessment Report

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		Cover page 4 8 9.3	Outcomes categories were: pregnancy outcomes, outcomes in live births, and maternal outcomes. Without modifying the outcomes themselves, they were recategorised as pregnancy outcomes, offspring outcomes, and maternal outcomes. In addition, the outcome labels were homogenised (eg, congenital anomalies and birth defects).	Outcome categories were modified to clarify the unit of analysis for each outcome. Outcome labels were homogenised for clarity.
		3	Updated principal investigator table	To account for study team updates
		4 6	The milestone section now provides one date for the start of the data collection and only one date for the end of data collection. The milestones also reflect that timelines might need to be modified depending on the dates of protocol endorsement.	Addressing comment 2 in CHMP/PRAC Final Assessment Report
		7.4	This is a new section in the background to describe findings from the literature pertaining to the study.	For completeness
		7	It is now explicit that lactation is investigated in the C4671039 PK study; the feasibility of studying lactation in the safety study will be subsequently assessed if substantial transfer into breast milk is found.	Addressing comment 4 in CHMP/PRAC Final Assessment Report
		Cover page 4 8	Objectives are now explicit in terms of what the comparator populations are for the pregnant women population.	Addressing comment 7 in CHMP/PRAC Final Assessment Report
		9.1.2	Discussion on drugs that could be used as active comparators (in addition to molnupiravir) has been added.	Addressing comment 8 in CHMP/PRAC Final Assessment Report
		4 9.1 12	The feasibility assessment for this programme was expanded to include a characterisation of the study populations by exposure status; this is to be included in interim reports.	Addressing comment 10 and comment 15 in CHMP/PRAC Final Assessment Report

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		9.1.1 9.2 9.2.1.1 9.2.1.2 9.9	Sections 9.2.1.1 and 9.2.1.2 were removed. Some text from those sections was relocated to Sections 9.1.1 (new in this protocol version) and 9.9. Inclusion and exclusion criteria were modified. Section 9.2 was restructured.	Addressing comment 14 in CHMP/PRAC Final Assessment Report
		9.1	Table 1 was restructured to remove the drug utilisation component and to reflect the study populations per the Agency´s request.	Addressing comment 11 in CHMP/PRAC Final Assessment Report
		9.1	The text related to target trial emulation in Section 9.1 was removed.	Addressing comment 12 in CHMP/PRAC Final Assessment Report
		9.2	The age-related inclusion criterion for safety analyses was removed (study participants had to be aged 18 years or older).	To include in the study a population as broad as possible
		9.2	The figure for the drug utilisation component was removed; the figure for the safety component was modified to reflect each population, as needed.	Addressing comments 13 and 15 in CHMP/PRAC Final Assessment Report
		9.2 9.9	Inclusion and exclusion criteria were modified to require documented COVID-19 from all individuals in the study; criteria are now stated as bullet points. The limitations associated with this inclusion criterion have been expanded.	Addressing comments 14 and 15 in CHMP/PRAC Final Assessment Report
		9.2	Pregnancy identification processes were described for each proposed data source.	Addressing comment 16a in CHMP/PRAC Final Assessment Report
		9.2.2	Table added to show the study period in each data source, incorporating lag and timing of data updates.	Addressing comment 17 in CHMP/PRAC Final Assessment Report
		9.3.2	Major congenital malformations will be identified using EUROCAT definitions.	Addressing comment 18 in CHMP/PRAC Final Assessment Report

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		9.3.2	Table 5 mentioned a sensitivity analysis that would consider all pregnancies (including all pregnancies with unknown outcome) to be pregnancy terminations. This sensitivity analysis was removed (it is retained in relation with spontaneous abortions).	This was an oversight in the previous version of the protocol; it had been decided that this analysis would be removed (it might increase the misclassification of terminations rather than decrease them)
		9.3.2	Column header in Table 5 was modified.	Addressing comment 20 in CHMP/PRAC Final Assessment Report
		9.3.3	The obstetric comorbidities, previously indicated through a reference, are now enumerated (from the same reference).	For clarity
		9.4	Information was added indicating that the Spanish data source BIFAP is not available for studies funded by pharmaceutical companies.	Addressing comment 23 in CHMP/PRAC Final Assessment Report
		9.4	This section was expanded to include new information on Paxlovid supplies to countries in the European Union.	For completeness
		9.5	Additional calculations on the estimated size of the study population and anticipated study precision for various outcomes was included.	Addressing comment 24 in CHMP/PRAC Final Assessment Report
		9.7	Propensity score matching with ratio up to 1:5 will be considered for control of confounding.	Addressing comment 25 in CHMP/PRAC Final Assessment Report
		9.7.2	For major congenital malformations, live birth and total prevalences per the EUROCAT definition will be calculated.	Addressing comment 26 in CHMP/PRAC Final Assessment Report
		Annex 3	A checklist for complete reporting in perinatal pharmacoepidemiology research was added. This is a new Annex.	For completeness

6. MILESTONES

Milestone	Planned/actual date
Protocol C4671037 V1.0 submission	31 May 2022 (actual; including pregnant population, population with moderate or severe hepatic impairment, and population with moderate or severe renal impairment in a single protocol)
Final CHMP/PRAC feedback	15 September 2022 (actual)
Protocol C4671037 V2.0 submission	November 2022 (pregnant population)
Regulatory protocol endorsement anticipated	Quarter 1 or quarter 2 2023
Registration in the EU PAS Register	Study will be registered prior to start of data collection
Progress report submission	November 2022
Start of data collection[a]	Quarter 4 2023[b]
Interim report 1	12 months after protocol endorsement; interim report 1 estimated for quarter 2 2024[b]
Interim report 2	24 months after protocol endorsement; interim report 2 estimated for quarter 2 2025[b]
End of data collection[a]	Quarter 2 2025[b]
Paediatric study report (as applicable if Paxlovid is used by pregnant individuals younger than 18 years old[3])	6 months after the end of data collection for the final report[b]
Final study report	28 November 2025[b]

Note: Contracts for study implementation between the sponsor and research organisation(s), data source selection, and approvals by data protection, data custodian, ethics, and scientific review bodies, several of which require a final or endorsed protocol, are pending. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised.

a. Start of data collection is "the date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts."[4] Simple counts are not part of this definition. End of data collection is "the date from which the analytical data set is completely available." [4]
b. Protocol endorsement is anticipated in quarter 1 or quarter 2 2023. Deliverable dates will be updated once protocol endorsement date is known.

7. RATIONALE AND BACKGROUND

Paxlovid contains nirmatrelvir (formerly PF-07321332) and ritonavir copackaged. Nirmatrelvir is an oral protease inhibitor that blocks the activity of 3-chymotrypsin-like cysteine protease, an enzyme required for the replication of SARS-CoV-2, the cause of coronavirus disease 2019 (COVID-19). Ritonavir slows the metabolism of nirmatrelvir in a way that allows nirmatrelvir to remain active in the body for longer periods of time and at higher concentrations. Nirmatrelvir is expected to retain activity against the Omicron variant.[5]

The safety of Paxlovid in pregnant women and in individuals with hepatic or renal impairment is not known. The studies on the safety of Paxlovid in pregnant women and in individuals with moderate or severe hepatic or renal impairment are regulatory commitments to the EMA. The safety of Paxlovid in pregnant women is also a regulatory commitment to the UK Medicines and Healthcare products Regulatory Agency (MHRA). This protocol addresses the safety of Paxlovid in pregnant women. Lactation is not included in the PASS of

pregnant women, but is investigated in the C4671039 pharmacokinetics study; if this study demonstrates transfer into breast milk to a relevant extent, then the feasibility of studying lactation in the safety study will be assessed.

This non-interventional study is designated as a PASS and is a commitment to EMA and MHRA.

7.1. Authorisations

On 22 December 2021, the US Food and Drug Administration issued an Emergency Use Authorization for Paxlovid.[6] On 31 December 2021, the UK MHRA issued a conditional marketing authorisation (CMA) for Paxlovid in Great Britain and a temporary Regulation 174 authorisation for Northern Ireland to ensure supply across all the UK.[7] Paxlovid was authorised for use in the European Union (EU) for the treatment of COVID-19 following the granting of a CMA by the European Commission on 28 January 2022.[8] When the EMA granted a CMA for Paxlovid, it applied in Northern Ireland, and the Regulation 174 authorisation is no longer in place.

7.2. European Union summary of product characteristics

The indication of Paxlovid in the EU is "for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19."[9] The recommended dosage is 300 mg of nirmatrelvir (two 150-mg tablets) and 100 mg ritonavir (one 100-mg tablet) taken together orally every 12 hours for 5 days. Paxlovid should be started as early as possible after the COVID-19 diagnosis and within 5 days of symptom onset. The 5-day treatment should be completed even if the patient requires hospitalisation due to COVID-19 progression after starting Paxlovid treatment.

Women of childbearing potential should avoid becoming pregnant during Paxlovid treatment and in the 7 days after completing the treatment course. Ritonavir may reduce the efficacy of combined hormonal contraceptives; patients who use them should be advised to use an effective alternative contraceptive method or an additional barrier contraception method during treatment and until the following menstrual cycle.

Regarding use in pregnancy, the SmPC indicates that no data exist from the use of Paxlovid in pregnant women. Lower foetal body weights were observed in rabbit tests with PF-07321332. The SmPC also indicates that Paxlovid is not recommended during pregnancy and in women of childbearing potential who do not use contraception, unless the clinical condition requires it. Regarding use in breast-feeding women, the SmPC indicates that no data are available on the use of Paxlovid in breast-feeding women and that "*it is unknown whether PF-07321332 is present in human or animal milk, and the effects of it on the breast-fed newborn/infant, or the effects on milk production. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breast-fed newborn/infant or on milk production. A risk to the newborn/infant cannot be*

excluded. Breast-feeding should be discontinued during treatment and as a precautionary measure for 7 days after completing Paxlovid."

7.3. United Kingdom summary of product characteristics

The indication of Paxlovid in the UK is: "*Paxlovid is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19,"*[10] like in the EU.

The UK SmPC states that women of childbearing potential should avoid becoming pregnant during treatment (no reference to any period after treatment) and recommends advising patients who use combined hormonal contraceptives to employ alternative contraceptive methods or a barrier method during treatment and until after 1 complete menstrual cycle afterward. In the UK SmPC, the recommendation against use in pregnancy is stronger than in the EU (*"Paxlovid is not recommended during pregnancy and in women of childbearing potential not using effective contraception"*), with no consideration of the patient´s clinical condition.

Like in the EU, the UK SmPC states that *"A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with Paxlovid and for 7 days after the last dose of Paxlovid."*

7.4. What is known

A research letter reported that 11 pregnant patients initially agreed to receiving Paxlovid after a consultation with a foeto-maternal specialist in a medical practice in the US between 16 April and 18 May 2022.[11] Four women did not initiate treatment. The 7 women who initiated treatment were aged 21 to 35 years and were diagnosed with COVID-19 at 9 to 37 weeks of gestation. Pre-existing conditions are not described in the publication; body mass index ranged from 22.4 to 41.2 kg/m^2 (it is unclear whether these were pregnancy values). One woman developed dysgeusia and stopped treatment; others continued treatment with no reported complications. Three women had delivered at the time of publication. The 3 infants were delivered vaginally at term; birth weights were 2390 g (labour induction due to cholestasis of pregnancy), 2960 g (gestational hypertension diagnosed shortly after delivery), and 3380 g. Other pregnancies were ongoing, and no other complications were reported.

8. RESEARCH QUESTION AND OBJECTIVES

The research question is: what are the prevalence and comparative safety of adverse pregnancy, offspring, and maternal outcomes in women exposed to Paxlovid during pregnancy?

The primary study objective is to estimate the birth prevalence, prevalence ratio, and prevalence difference of the following adverse pregnancy, offspring, and maternal outcomes in women who are exposed to Paxlovid during pregnancy compared with those in women

who are exposed to molnupiravir, where available, during pregnancy or to neither Paxlovid nor molnupiravir during pregnancy:

Pregnancy outcomes

- Spontaneous abortion
- Elective termination
- Stillbirth
- Preterm delivery

Offspring outcomes

- Major congenital malformations
- Intrauterine growth retardation/small for gestational age

Maternal outcomes

- Gestational diabetes
- Postpartum haemorrhage
- Maternal death

9. RESEARCH METHODS

9.1. Study design

The study population is described in Table 1.

Table 1. Study population

Study population	General description
Women who are pregnant and have COVID-19 (and their offspring where appropriate)	The process for identifying pregnancies and pregnancy start dates is specific to each data source. Included in the study will be users of Paxlovid, users of the comparator medication molnupiravir (when available), and the unexposed pregnant individuals who are at increased risk for progression to severe COVID-19.

The study will have a cohort design and will make secondary use of multiple sources of data from electronic health records and/or claims data in European countries. Data sources currently selected have the ability to capture Paxlovid exposure where the target populations, study outcomes, and key covariates can be ascertained.

The feasibility component of this research programme will provide counts of the target population, separately for Paxlovid users, users of molnupiravir, and the unexposed comparator group. Relevant patient characteristics will be presented for each exposure group in the target population to allow an assessment of the feasibility of comparative analyses.

Molnupiravir has been preliminarily selected as an active comparator for this study because its indication is similar and users are anticipated to be comparable to Paxlovid users in terms of COVID-19 severity at treatment start and risk for progression to severe COVID-19[12] (see additional discussion in Section 9.1.1). At the time of preparing this protocol, molnupiravir was not utilised in the populations covered by some selected data sources or its use was not captured by the data sources (eg, France and Information System for Research in Primary Care [SIDIAP] in Catalonia, Spain). Therefore, a second comparator group is included in the study: individuals who were at increased risk for progression to severe COVID-19 and had not received Paxlovid, molnupiravir, or any other antiviral treatment. Challenges are discussed in Section 9.9. Strategies to reduce confounding will be applied. Briefly, individuals will be described, and safety outcomes will be assessed in comparative analyses. Pooling of results using meta-analytic techniques is planned. Analyses are outlined in Section 9.7, and details will be included in the statistical analysis plan (SAP).

Reports will include a progress report with a description of project start-up and subsequent activities, the evolution of the identified challenges for this study, and the list of anticipated data sources (per an ongoing feasibility assessment on Paxlovid distribution channels in various countries); 2 annual interim reports with results of the feasibility component (described previously) and preliminary outcome counts; a final report with the results of the safety component; and, if applicable, i.e., if pregnant individuals aged younger than 18 years[3] use Paxlovid, a paediatric report 6 months after the end of data collection for the final report.

A checklist to confirm that all key methods elements for perinatal pharmacoepidemiology research are addressed explicitly in this protocol is included in Annex 3.

9.1.1. Discussion of molnupiravir as an active comparator

Molnupiravir was not authorised in the EU at the time of writing this protocol. However, EMA issued advice indicating that it could be used, like Paxlovid, to treat adult patients with COVID-19 who do not need supplemental oxygen and who are at increased risk for progression to severe COVID-19.[12] Like Paxlovid, molnupiravir is to be administered within 5 days of symptom onset and taken for 5 days. Molnupiravir should not be administered in pregnancy or to individuals who can become pregnant and are not using contraception.[12] Some countries in the EU, eg, Italy, have made it available for use,[13] and the Spanish Health Agency included it among available treatment options.[14] Molnupiravir was approved by the MHRA in the UK in November 2021.[15] The approved indication is consistent with the language in EMA's advice described above.[16]

Because of the similar indication and mode of use, molnupiravir users are anticipated to be comparable to Paxlovid users in terms of COVID-19 severity at treatment start and risk for

progression to severe COVID-19. Molnupiravir can be used in patients with hepatic or renal impairment, which can result in channelling of patients with these problems to molnupiravir and away from Paxlovid. This was confirmed in OpenSAFELY data: 0.7% of Paxlovid users had liver disease and less than 0.5% had kidney disease, while 4.9% of molnupiravir users had liver disease and 11.2% had kidney disease.[17]

9.1.2. Discussion on other drugs to treat COVID-19 as potential active comparators

Other drugs that are used to treat COVID-19 have characteristics that make them less than optimal comparators for this study. Details are presented in Table 2. Other drugs that may be approved before the final analyses start will be assessed for suitability as additional comparators.

Table 2. Other EMA-approved drugs to treat COVID-19

Drug	Indication and mode of administration	Pregnancy	Comments
Remdesivir[18]	• Adults and children with pneumonia requiring supplemental oxygen • Adults and children who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19 • Intravenous	Should not be used during pregnancy; women of childbearing potential must use effective contraception during treatment	• Second indication comparable to that of Paxlovid • Intravenous medications are expected not to be well captured in the proposed data sources (which were selected based on the known distribution of Paxlovid)
Tixagevimab/ cilgavimab[19]	• COVID-19 preexposure prophylaxis in adults and adolescents • Treatment of adults and adolescents with COVID-19 who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19 • Intramuscular[19] or intravenous[20]	Should be used in pregnant women only if the potential benefit to the mother justifies the potential foetal risk	• Second indication comparable to that of Paxlovid • If use of this product were captured for its treatment indication, it could be included among potential comparators
Anakinra[21]	• Rheumatoid arthritis, periodic fever syndromes, familial Mediterranean fever, and other conditions • COVID-19 treatment in adults with pneumonia requiring supplemental oxygen who are at risk for progressing to severe respiratory failure determined by plasma levels ≥ 6 ng/mL of soluble urokinase plasminogen activator receptor • Subcutaneous injection	Avoid the use during pregnancy and in woman of childbearing potential not using contraception	The multiple indications and the COVID-19 indication for patients who have a more severe COVID-19 than those anticipated to receive Paxlovid, and the fact that the COVID-19 use might be in hospitalised patients, make this product not suitable as a comparator drug
Regdanvimab[22]	• Treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19 • Intravenous infusion	Should be used in pregnant women only if the potential benefit to the mother justifies the potential foetal risk	Intravenous medications are expected to be not well captured in the proposed data sources

Table 2. Other EMA-approved drugs to treat COVID-19

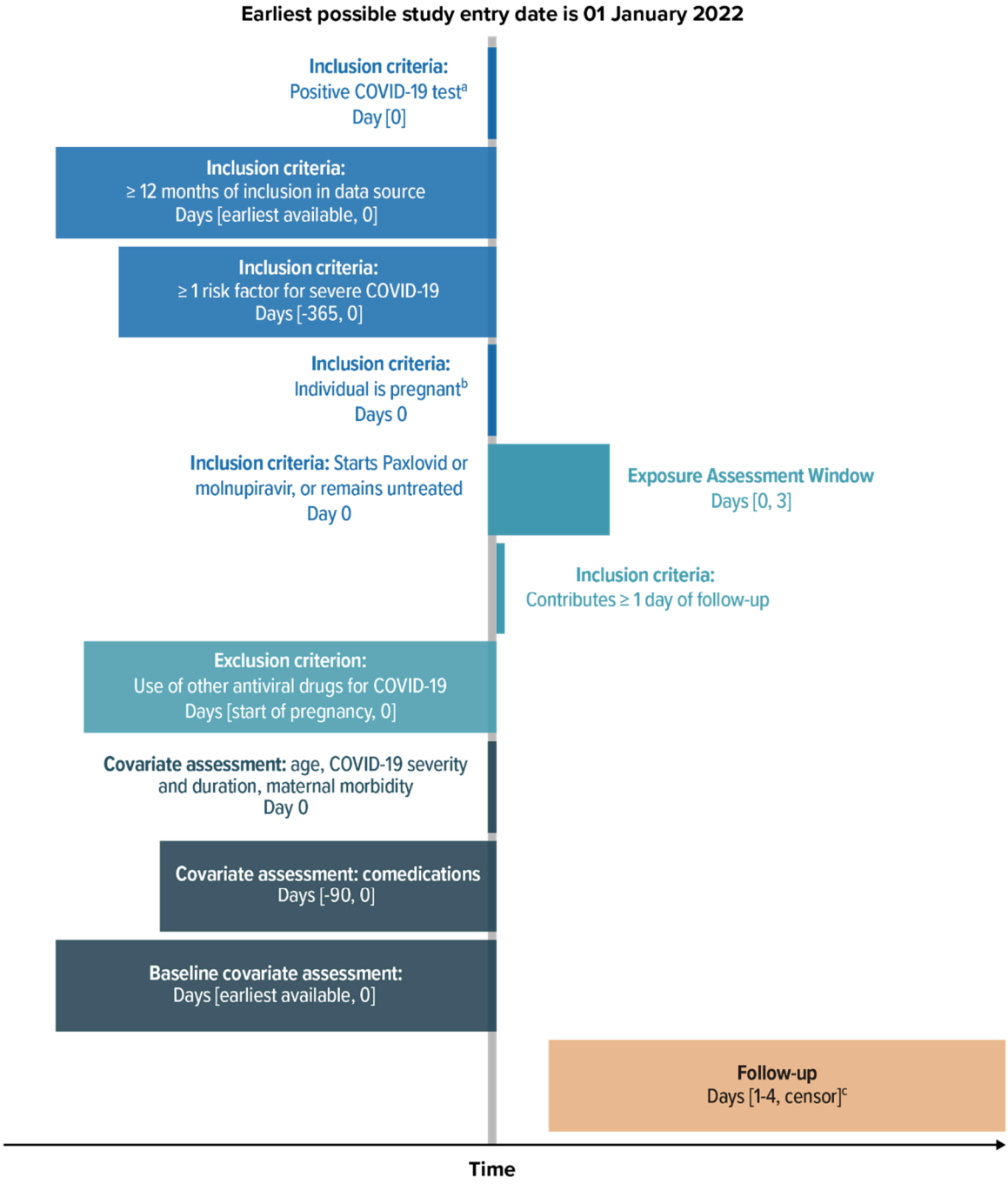
Drug	Indication and mode of administration	Pregnancy	Comments
Tocilizumab[23]	• Rheumatoid arthritis, juvenile idiopathic polyarthritis, and other conditions • Treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation • Intravenous infusion	Should not be used in pregnancy unless necessary	The multiple indications and the fact that the COVID-19 use might be in hospitalised patients make this product not suitable as a comparator drug
Casirivimab / imdevimab[24]	• COVID-19 postexposure prophylaxis • Treatment of COVID-19 in adults and adolescents who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19 • Intravenous infusion or subcutaneous injection	Use only if the potential benefit justifies the potential risk for the mother and the foetus	• Second indication comparable to that of Paxlovid • If use of this product were captured for its treatment indication, it could be included among potential comparators
Sotrovimab[25]	• Treatment of adults and adolescents with COVID-19 who do not require oxygen supplementation and are at increased risk for progression to severe COVID-19 • Intravenous infusion	Should be used only if the expected benefit to the mother justifies the potential foetal risk	Intravenous medications are expected to be not well captured in the proposed data sources

Source of drug list: EMA, COVID-19 treatments. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-.vaccines/covid-19-treatments. Accessed 6 October 2022.

9.2. Setting

Figure 1 provides an overview of the data elements that will be ascertained for eligibility and the timing of ascertainment. Additional details are provided in the following sections.

Figure 1. Overview of the timing for covariate ascertainment



[a] Including positive test, documented diagnosis or documented entry in a COVID-19 registry, reflecting a COVID-19 diagnosis. The prespecified period for the positive test is 3 days, starting the day after the date of the test, diagnosis or registration, and before the day of starting treatment (among the treated) or starting follow-up (among the unexposed).
[b] Each woman needs to be pregnant at day 0 for inclusion; for pregnancy outcomes that require information on end of pregnancy, only pregnancies with known outcome will be included.
[c] For pregnant women, follow-up will end at the earliest of death, disenrollment/migration, or 1 week after the end of pregnancy, end of data availability, 6 months after pregnancy, or treatment group crossover; for offspring outcomes, offspring follow-up will continue through the earliest of death, disenrollment or migration, end of data availability, or the end of the first year of life.
Note: Figure based on Schneeweiss et al.[26]

9.2.1. Inclusion criteria, exclusion criteria, and follow-up

Inclusion and exclusion criteria

This target population will comprise pregnant individuals with documented COVID-19 and increased risk for progression to severe COVID-19 who had at least 12 months of inclusion in the data source population and were users of Paxlovid or comparator medication molnupiravir or remained unexposed. At least 1 day of follow-up will be required for inclusion in the study. Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Woman is pregnant (no age restriction) at the time of COVID-19 diagnosis
2. Woman has documented COVID-19
3. Woman has increased risk for progression to severe COVID-19
4. Woman has at least 12 months of inclusion in the data source at the time of starting the study medications or becoming eligible
5. Woman started treatment with Paxlovid or comparator medication within 3 days of the COVID-19 diagnosis or did not start those treatments during that period
6. Woman contributed at least 1 day of follow-up. Women who test positive at screening at hospital admission for delivery will not be included in the study population, as they will not contribute to follow-up.

Exclusion criterion

Patients meeting any of the following criteria will not be included in the study:

1. Woman received Paxlovid, comparator medication, or other medications listed in Table 2 earlier in the pregnancy

Pregnancies with foetuses with major or minor malformations or chromosomal abnormalities, and multifetal pregnancies will be included in the study. Women can contribute more than one pregnancy to the study.

After the eligibility criteria are applied, the target population will include pregnant individuals starting Paxlovid or molnupiravir during the study period and unexposed pregnant individuals.

Time 0 will be the day on which individuals meet all eligibility criteria; they will have 3 days to start treatment with Paxlovid or molnupiravir (this is often described as a grace period). Unexposed individuals will be matched with individuals starting Paxlovid by time since COVID-19 diagnosis (days) and calendar time (within ± 1 week). Paxlovid and molnupiravir users will be matched on calendar time. Matching at this stage has the objective of increasing comparability of treatment groups regarding time since start of disease and calendar time (calendar time is a proxy for prevalence of circulating variants, preferred therapeutic approaches, etc.).

Follow-up

Follow-up of pregnant women will start between day 1 (the day after time 0) and day 4, depending on which day exposure or unexposure assignment (via matching) starts. Follow-up will end at the earliest of 6 months after end of pregnancy, death, disenrollment or migration, end of data availability in the data source, or treatment group crossover. *Treatment crossover* is defined in this study as the situation in which individuals who entered the study as unexposed start treatment with Paxlovid or molnupiravir, when molnupiravir users start treatment with Paxlovid, or when Paxlovid users start treatment with molnupiravir. The 6 months after the end of pregnancy will be used to assess pregnancy outcomes. Follow-up of the offspring to assess offspring outcomes will continue through the earliest of death, disenrollment or migration, end of data availability in the data source, or 1 year of age. Follow-up for each outcome will end at the occurrence of the given outcome. Starting treatment with drugs to treat COVID-19 that are not Paxlovid or comparator drug molnupiravir will not result in censoring.

Pregnancy identification

The process of identifying pregnancies and pregnancy start dates is specific to each data source. In some data sources (eg, SNDS), pregnancies are identified only when they end because the records available for research include only information that is generated at that time (eg, via a birth registry). In other data sources (eg, CPRD), pregnancies can be identified using both records for pregnancy outcomes and records for ongoing pregnancies, such as codes for diagnostic tests and services that are indicated only during pregnancy.[27] The latter is the preferred approach for this study and will be used to the extent possible. When using records for ongoing pregnancies, pregnancies with unknown outcome will be identified, including pregnancies whose expected date of delivery is after the last available date in the data cut (likely ongoing pregnancies) and pregnancies for which delivery has occurred but the outcome is not documented in the data source. Reasons why pregnancy outcomes may

not be documented after the delivery date among individuals who continue to be present in the data source include missing data (eg, delivery occurred in a hospital and is not or is not yet documented in primary care records [if using primary care data]) or because the pregnancy ended in an elective termination or spontaneous abortion and is not documented in the data source.[27,28] In some data sources (such as CPRD), one can assume that a large proportion of the pregnancies that started well before the end of data availability and have an unknown outcome are spontaneous abortions.[29] This will be addressed in a sensitivity analysis on the outcome definitions (Section 9.7).

Pregnancy identification and mother-infant linkage in SNDS (France)

Algorithms are available in SNDS to identify pregnancies and to link mothers to infants.[30,31] The pregnancy identification algorithm identifies pregnancies based on discharge diagnoses and medical procedures associated with pregnancy outcomes (live births, stillbirths, elective abortions, therapeutic abortions, spontaneous abortions, and ectopic pregnancies) recorded in the French national insurance database (DCIR) or the French hospital discharge database (PMSI). To differentiate records associated with separate pregnancies, a minimal interval is required between consecutive pregnancies, depending on the outcome type. Information on gestational age, the date of the first prenatal medical examination, dates of the ultrasounds, and date of the pregnancy outcome can be used to estimate the dates of the beginning and end of pregnancy. Linkage between maternal and neonatal data for births occurring at or later than 22 weeks of gestation is possible within the PMSI using a common identifier that is recorded for both the delivery stay and the birth stay. Follow-up of infants after birth is possible through linkage of the infant to the social security numbers of the parents.

Pregnancy identification and mother-infant linkage in SIDIAP (Spain)

An algorithm to identify pregnancies has been previously used within SIDIAP.[32-34] The algorithm uses diagnosis codes recorded in primary healthcare records during pregnancy and information recorded in the sexual and reproductive healthcare registries, including first day of the last menstrual period (LMP), gestational week, expected date of delivery, actual date of delivery or termination, and pregnancy outcomes. Approximately 50% to 60% of pregnant women in Catalonia are attended in the sexual and reproductive healthcare centres that contribute data to SIDIAP. Approximately 70% of infant records can be linked to maternal records and used for research.

Pregnancy identification and mother-infant linkage in CPRD Aurum (UK)

CPRD has developed algorithms for pregnancy identification and mother-infant linkage.[35,36] The pregnancy identification algorithm uses SNOMED CT (Systematized Nomenclature of Medicine--Clinical Terms) codes, Read codes, data source–specific identifiers for antenatal care, pregnancy outcomes (including delivery and pregnancy loss), and postnatal care to identify patients who have had a pregnancy. The pregnancy identification algorithm first classifies pregnancy outcome records into distinct pregnancy episodes (combining multiple records related to the same pregnancy). The start of each of pregnancy is then estimated based on information on gestational age, estimated date of delivery, estimated date of

conception, or LMP (if available) or is imputed based on a default gestational age (depending on the outcome type). Next, additional pregnancies without an outcome recorded are identified using antenatal records. For pregnancies without a recorded outcome, pregnancy end is estimated using the latest record during the pregnancy, and pregnancy start is estimated based on information on gestational age, estimated date of delivery, estimated date of conception, or LMP (if available) or by subtracting 4 weeks from the earliest antenatal record during the pregnancy.

Mother-infant linkage within the CPRD is conducted using a probabilistic algorithm that uses data recorded in the primary care medical record.[37] Mother-infant pairs are linked using family number (which identifies individuals within the same family), maternity information from the mother's primary care record (used to identify deliveries and delivery dates), and the birth month/year of newly registered infants.

The cited papers refer to the process implemented in General Practitioner Online Database (of CPRD) (CPRD GOLD); the same references are provided by CPRD to describe the process implemented in CPRD Aurum.

9.2.2. Study period

The study period will start on 01 January 2022 (in alignment with regulatory authorisation in Europe) and end as late as possible, with final data extraction estimated for quarter 1 2025.

Table 3 shows the anticipated dates during which data will be observed for each study report.

Table 3. Dates for start of study period and end of data availability for each study report in each data source

Data source	Start of study period	Anticipated end of data availability		
	Date of authorisation: 01 January 2022	Interim report 1	Interim report 2	Final report
CPRD Aurum	01 January 2022	Q3 2023	Q3 2024	Q4 2024
SIDIAP	01 January 2022	30 June 2023	30 June 2024	30 June 2024
SNDS	01 January 2022	31 December 2022	31 December 2023	31 December 2023

Note: Interim report 1 has an anticipated data cut in Q4 2023; interim report 2, in Q4 2024; final report, in Q1 2025.

9.3. Variables

9.3.1. Exposure

The main exposure of interest will be Paxlovid, which will be ascertained from prescription and pharmacy information reflecting prescriptions issued (eg, CPRD) or dispensed (eg, French Administrative Healthcare Database [SNDS]) or from other data sources (eg, a

central Paxlovid distribution registry if Paxlovid distribution is documented in this manner). See Section 9.4 for details.

The periods of pregnancy during which exposure will be ascertained (often described as exposure windows) are specific to each outcome, reflecting the period at risk for each outcome; they are listed in Section 9.3.2.

9.3.2. Outcomes

The outcomes will be those listed in Table 4. They will be ascertained using coded diagnoses, procedures, medical product prescriptions or dispensings, and information collected in other data banks in the selected data sources. Validated algorithms for outcome identification, if available, will be used. To further explore validity and adjust algorithms as needed for selected study outcomes, a random sample of patient profiles, i.e., the electronic information ordered chronologically, could be reviewed.

A more detailed description of the subsets of pregnancies among which each outcome will be ascertained is presented in Table 5.

In this study, the first occurrence of each outcome during follow-up will be considered a study outcome, and outcome occurrence will determine end of follow-up for that outcome, as described in Section 9.2.1.

Table 4. Study outcomes in the target population

Study population	Study outcomes
Individuals who are pregnant (and their offspring, as appropriate)	Pregnancy outcomes • Spontaneous abortion • Elective termination • Stillbirth • Preterm delivery (all, iatrogenic, and spontaneous) Offspring outcomes • Major congenital malformations • Intrauterine growth retardation/small for gestational age Maternal outcomes • Gestational diabetes • Postpartum haemorrhage • Maternal death

Table 5. Identification of pregnancy-related outcomes and outcome-specific exposure windows

Outcome	Description of outcome and outcome-specific exposure window	Pregnancies among which the outcome will be ascertained	Source records
Spontaneous abortions	Foetal loss before 20 completed weeks of gestation. The period during which this outcome can occur is before 20 completed weeks; individuals will be considered exposed if drug use occurs during this period. Sensitivity analysis: In data sources where we can assume that pregnancies with unknown outcome are neither live births nor stillbirths, in a sensitivity analysis, all pregnancies with unknown outcome and an estimated delivery date of ≥ 3 months before data extraction among women included in the data source at the time of data extraction will be considered a spontaneous abortion.	All pregnancies with known outcome; for sensitivity analysis, all pregnancies	Maternal records
Elective terminations	Nonspontaneous termination of pregnancy, including ectopic pregnancies, termination due to foetal anomalies or any other cause. The at-risk period for this outcome is the time during which these can occur, which varies by jurisdiction. Because it is expected that elective terminations will occur in early pregnancy, the at-risk period will be before 20 completed weeks; individuals will be considered exposed if drug use occurs during this period.	All pregnancies with known outcome	Maternal records
Stillbirths	Foetal loss on or after 20 completed weeks of gestation. The period during which this outcome can occur is on or after 20 completed weeks; individuals will be considered exposed if drug use occurs any time during pregnancy.	All pregnancies with known outcome Although pregnancies that end earlier than 20 completed weeks are not at risk for this outcome, the outcome will be ascertained among all pregnancies with known outcome for comparability with other studies.	Maternal records
Preterm delivery	Live birth before 37 completed weeks Individuals will be considered exposed if drug use occurs before 37 completed weeks.	Pregnancies ending with live birth	Maternal records
Preterm delivery: iatrogenic	This is the subset of preterm deliveries in which the delivery is initiated for maternal or foetal conditions.	Pregnancies ending with live birth	Maternal records
Preterm delivery: spontaneous	These are the remaining preterm deliveries.	Pregnancies ending with live birth	Maternal records

Table 5. Identification of pregnancy-related outcomes and outcome-specific exposure windows

Outcome	Description of outcome and outcome-specific exposure window	Pregnancies among which the outcome will be ascertained	Source records
Major congenital malformations	Structural changes with significant medical, social, or cosmetic consequences for the affected individual that typically require medical intervention.[38] The EUROCAT definitions will be followed.[39] Minor (per the EUROCAT classification[38]) and unspecified anomalies; chromosomal abnormalities, genetic syndromes or sequences; or endocrine, metabolic, immunologic, or haematologic anomalies will not be included in this definition. Organogenesis occurs during the first trimester; individuals will be considered exposed if drug use occurs before or at completed week 13 from the LMP.	All pregnancies resulting in a live birth Congenital anomalies can occur in pregnancies that end in other pregnancy outcomes, but no information is typically available regarding the presence of congenital anomalies in stillbirths or spontaneous abortions.	Maternal and infant records
Intrauterine growth retardation/ small for gestational age	Foetal or birth weight below the 10th percentile for gestational age and sex Individuals will be considered exposed if drug use occurs any time during pregnancy (and before the first code indicating the presence of the outcome).	Pregnancies ending with live birth	Maternal and possibly infant records (depending on the data source)
Gestational diabetes	Diabetes that is first diagnosed during pregnancy Individuals will be considered exposed if drug use occurs any time during pregnancy (and before the first code indicating the presence of the outcome).	All pregnancies reaching the gestational age at which diagnosis is typical (eg, 24 completed weeks)	Maternal records
Postpartum haemorrhage	Abundant haemorrhage after delivery; will be ascertained from delivery to 6 days after delivery. Individuals will be considered exposed if drug use occurs any time during pregnancy.	All pregnancies with known outcome	Maternal records
Maternal death	Death during pregnancy Individuals will be considered exposed if drug use occurs any time during pregnancy.	All pregnancies	Maternal records

9.3.3. Other variables

In addition, the following study variables will be included:

- Demographics
- Comorbidities and characteristics that will be quantified to identify increased risk for progression to severe COVID-19, including cancer diagnoses or treatments, chronic

kidney disease (CKD), chronic liver disease, chronic respiratory disease, cardiovascular or cerebrovascular disease, obesity, Down syndrome, mental health conditions, sickle cell disease, diabetes, human immunodeficiency virus (HIV) infection and use of immunosuppressants.[40] Increased risk for progression to severe COVID-19 will be ascertained in the 12 months before drug initiation or Paxlovid eligibility (as appropriate).

- For the purpose of this PASS, individuals at increased risk for progression to severe COVID-19 will be individuals with COVID-19 diagnosis or registration in a COVID-19 registry and at least 1 risk factor listed in the previous bullet point (acknowledging that prescribing physicians may not base their assessment on exactly these variables).

- Characteristics to identify maternal morbidity: preeclampsia/eclampsia, chronic congestive heart failure, congenital heart disease, pulmonary hypertension, chronic ischaemic heart disease, sickle cell disease, multifetal gestation, cardiac valvular disease, systemic lupus erythematosus, HIV, drug abuse, placenta previa, chronic renal disease, pre-existing hypertension, previous C-section, gestational hypertension, alcohol abuse, asthma, pre-existing diabetes mellitus.[41]

- Comedications, including medications listed as contraindicated or with potentially significant interactions with Paxlovid in the EU SmPC,[9] Section 4.3 and Table 1, or the UK SmPC,[10] Table 1 and Table 2. Use of these medications will be quantified in the 3 months before Paxlovid use to provide information on the number of patients who may be at risk for simultaneous use of Paxlovid and these medications; please see caveats in Section 9.9.

- COVID-19 diagnoses, days since current infection, COVID-19 severity at start of treatment.

- COVID-19 vaccination status, as available.

Baseline information will be obtained from records before drug initiation or Paxlovid eligibility.

9.4. Data sources

As of 20 September 2022, the MAH confirmed that Paxlovid has been supplied to France, Germany, Italy, Spain, Slovenia, Sweden, and the UK, initially or continuing under special government contracts, resulting in different distribution and reimbursement channels being used and subsequent challenges capturing its prescription and distribution. Current information is that prescribed/dispensed Paxlovid should be captured in existing electronic population data sources in France, Spain, and the UK. Currently, the proposed data sources are SNDS (France), SIDIAP (Catalonia, Spain), and CPRD Aurum (UK). Exposure counts are presented in Table 6.

Table 6. Study feasibility: Paxlovid distribution in Europe

Country	Capture in data sources
France	Medic'AM : 12,634 dispensed boxes in February-June 2022 EPI-PHARE report: 12,179 individuals received Paxlovid between 4 February and 29 June 2022[42]
Germany	Not available
Italy	AIFA Registry: 81,709 treatments as of 2 November 2022
Slovenia	Not available
Spain	SIDIAP: 353 Paxlovid prescriptions for 339 individuals from 7 April to 30 June 2022
Sweden	Not available at this point.
United Kingdom	CPRD Aurum: 400 prescriptions as of 13 September 2022 OpenSAFELY: 10,850 individuals as of 7 October 2022[17]

In France, Paxlovid received early access authorisation on 20 January 2022 and has been made available for prescription since 03 February 2022[43] in outpatient settings (a specific procedure needs to be completed by general practitioners and community pharmacists) and inpatient settings (including emergency care). To date, only dispensings from the outpatient setting (community pharmacies) are captured in SNDS; for inpatients and emergency room visits, the drug is directly provided to the hospital by health authorities, and patient exposure is not captured. Molnupiravir is not available in France.

In Spain, dispensing of Paxlovid is taking place in community pharmacies through validated prescriptions; it is expected that all Paxlovid prescriptions will be captured. The Spanish Medicines Agency of Medicines and Medical Devices (Agencia Española de Medicamentos y Productos Sanitarios [AEMPS]) informs that novel antivirals are distributed through the normal channels.[14] For Paxlovid (authorised), due to the interactions and special warnings for use, a special validation is required. Each autonomous region (eg, Catalonia) establishes its own validation, and the validation process should be shorter than 24 hours. Molnupiravir is not approved, but in case its use is considered, access will be on a case-by-case basis through an application for special use of medications. For patients eligible for antivirals, the AEMPS treatment graph indicates that they can be treated with Paxlovid or remdesivir or, alternatively, with molnupiravir. SIDIAP will contribute data (from Catalonia) to this study. BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atención Primària),

which collects longitudinal medical records from various regions in Spain and is administered by AEMPS, is not available for studies funded by pharmaceutical companies.

The Italian Medicines Agency (AIFA) established a national registry for Paxlovid and other antivirals for COVID-19. At this time, and while direct Italian government funding rather than funding through individual region occurs, capture of Paxlovid dispensing/prescriptions in the established electronic data sources that are commonly used for PASSs in Italy (eg, regional or local health unit data sources) is expected to be minimal. Initially, Paxlovid could only be prescribed and dispensed in selected centres in each Italian region (modality 1). As of April 2022, Paxlovid can be dispensed in pharmacies with a prescription also by general practitioners (modality 2). The counts, but not the clinical characteristics of the patients receiving Paxlovid under modality 2 are captured in the AIFA registry (D Striano, Pfizer Italy, email communication, 13 May 2022).

As long as the German government continues to cover Paxlovid payments, it is expected that Paxlovid prescriptions will not appear in the German Statutory Health Insurance data sources, which is based on prescriptions reimbursed by the insurers.

Slovenia had a very small supply (about 1000 packs), leading to a very small study size.

In Sweden, Paxlovid will be prescribed and distributed in hospitals, and therefore will not be captured in the Swedish registers typically used for pharmacoepidemiology research.

The UK OpenSAFELY data source is proposed for exploration as a supplementary data source for the PASS. The AIFA national registry for antivirals for COVID-19 is proposed for exploration as a source for the feasibility information in Italy.

The MAH will share additional information about Paxlovid supply and forecast for other European countries as it becomes available, and the research team will evaluate whether this allows capture of Paxlovid in additional electronic data sources in these countries.

9.4.1. France: French Administrative Healthcare Database (SNDS)

SNDS contains individual-level pseudonymised information on all outpatient reimbursed claims from all main French healthcare insurance schemes linked to the national hospital discharge summaries database and the national death register. It currently covers the overall French population—about 67 million individuals—from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires, capturing data from 2011.[44] Medical history data goes back to 2006 for 86% of the population. The following information is available for each individual:

- Demographics and general information: sex, date of birth, area/region of residence. Socioeconomic status can be derived from the presence of CMUc (*Couverture médicale universelle complémentaire*), which indicates full insurance coverage due to low-income status and deprivation index and a composite indicator that gives information on patient socioeconomic status based on its geographic residence.

- Registration for chronic conditions and date of first diagnosis of the condition: These conditions are itemised in a list of 3448 *International Statistical Classification of Diseases, Tenth Revision* (ICD-10) codes (Affections de Longue Durée [ALD]). Registration with an ALD is obtained at the request of a patient's practitioner and is validated by the health insurance system physician. Registration of chronic conditions may not be complete because patients are already registered for a related disease, or because the treatment is cheap, or because of stigma concerns.

- Occupational accidents and diseases.

- Medication dispensed in primary or secondary outpatient pharmacies, recorded as dispensed preparation packs, with dates (prescription and dispensing): Drug information includes ATC (Anatomical Therapeutic Chemical) code, CIP (Presentation Identifier Code) code (French pharmacy coding system), and EPhMRA (European Pharmaceutical Market Research Association) code; description of packs in number of tablets and strength; the number of packs dispensed; date of prescription and nature of prescriber, date of dispensing, and the dispensing pharmacy (anonymised). Information on underlying medical indication is not available.

- Medication dispensed in-hospital, recorded as dispensed units, with dates: available only for drugs prescribed out of the cost-coding system, mainly expensive drugs (eg, targeted cancer therapies and monoclonal antibodies). Drug information includes ATC code, UCD (common dispensing unit) code, and EPhMRA code. Information on underlying medical indication is not available.

- Date and nature of physician and paramedical (nurses, physiotherapist) encounters with procedures; outpatient diagnoses are not recorded.

- Date and nature of all laboratory test requests, without results.

- Hospital discharge summaries from PMSI (French national hospital discharge summaries database system): ICD-10 diagnosis codes for main and associated diagnoses for all medical, obstetric, and surgical hospitalisations, including date and duration of hospitalisation, medical procedures, diagnosis-related group, and the cost-coding system.

- Medical history data: available going back to 2006 for 86% of patients and to 2011 for all patients in the SNDS database.

- Date of death, through linkage with the national death registry, without the cause of death. [44]

- There is a well-defined algorithm to identify pregnancies and deliveries in SNDS only when they end. Mother-child linkage has been available in the SNDS since 2012, allowing identification of the newborn and follow-up within the database to conduct long-term pregnancy safety studies.[30,31]

Exposure to COVID-19 vaccines will be obtained through a linkage of the SNDS to the SI Vaccin COVID, the information system implemented by the Caisse Nationale de l'Assurance Maladie (CNAM), to enable the preparation, management, and monitoring of the COVID-19 vaccination campaign. It captures, among other things, vaccine brand and date of injection.[45]

If possible, results of all antigenic and reverse transcription polymerase chain reaction (RT-PCR) COVID-19 tests carried out in France—whether positive or negative—will be retrieved from the National Population Screening Information System (SI-DEP), a secure platform resulting from a partnership between the Ministry of Solidarity and Health, Public Assistance–Paris Hospitals. Linkage of the SI-DEP to the SNDS is currently ongoing at the national level under the supervision of CNAM.[46] While the linkage of the SI-DEP to the SNDS has been anticipated by the French law, issues related to the linkage are being addressed. The SNDS data holder is currently working on improving the linkage process, but the release date has not been communicated yet. The fact that a test has been performed is well captured by the database even in the absence of this linkage.

Outpatient diagnoses are not captured in the SNDS.

By law, it is not possible to go back to the patient to collect additional information. Most outcomes are identified with hospital diagnosis codes. For some studies, independent expert validation using reconstituted electronic health records using all information in the database, i.e., assembling a chronological listing of diagnoses, procedures, and medications recorded for a patient, can be conducted.[47]

Complete and consolidated SNDS data are released in the third quarter of the following year included in each period. Access to SNDS data is strictly regulated by French law and needs approval from the committee on health data research (Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé [CESREES]) and from the French Data Protection Commission (CNIL). The process typically requires 6 to 12 months before data extraction by the CNAM database operator: 3 to 5 months are required for this regulatory process, and 3 to 6 months to receive the extracted data. Data extraction requests at several timepoints over the study period can be anticipated from the study protocol, eg, once every year until the end of the study.

9.4.2. Spain: Catalan Information System for Research in Primary Care (SIDIAP)

SIDIAP was created in 2010 by the Catalan Health Institute and the IDIAP Jordi Gol Institute (IDIAP). It includes information collected since 01 January 2006 during routine visits at 278 primary care centres that are part of the Catalan Health Institute in Catalonia (northeast Spain), which has 3414 participating general practitioners. SIDIAP has

pseudoanonymised records for 5.7 million individuals (80% of the Catalan population) and is representative of the Catalan population.

The SIDIAP data comprise the clinical and referral events registered by primary care health professionals (eg, general practitioners, paediatricians, gynaecologists, and nurses) and administrative staff in electronic medical records, comprehensive demographic information, community pharmacy invoicing data, specialist referrals, and primary care laboratory test results. The SIDIAP data can also be linked to other data sources, such as the hospital discharge database, on a project-by-project basis. Health professionals gather this information using ICD-10 codes, ATC codes, and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, and blood and urine test results. SIDIAP includes all routine childhood and adult immunisations, including the antigen and the number of administered doses. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP database. The SIDIAP database is updated every 6 months, in January and July.

Recent reports have shown SIDIAP data to be useful for epidemiological research. SIDIAP is listed under the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources database (https://www.encepp.eu/encepp/viewResource.htm?id=4646).

Information on pregnancy and pregnancy outcomes recorded by gynaecologists and midwives is available from the ASSIR registers (sexual and reproductive healthcare registers). Approximately 50% to 60% of pregnant women in Catalonia are attended in the sexual and reproductive healthcare centres, where pregnancy-related information, including dates of pregnancy start and end, pregnancy outcomes, and other information, is captured. Approximately 70% of infant records can be linked to maternal records and used for research.

Study applications need to be approved by the SIDIAP Scientific Committee and the IDIAP Ethics Committee.

9.4.3. United Kingdom: Clinical Practice Research Datalink (CPRD) Aurum and Hospital Episode Statistics

CPRD in the UK collates the pseudonymised computerised medical records of general practitioners, who act as the gatekeepers of healthcare and maintain patients' life-long electronic health records. Accordingly, general practitioners are responsible for primary healthcare and specialist referrals, and they also document information about specialist referrals and hospitalisations. General practitioners act as the first point of contact for any non-emergency health-related issues, which may then be managed within primary care and/or referred to secondary care, as necessary. Secondary care teams also provide information to general practitioners about their patients, including key diagnoses. The data recorded in CPRD include demographic information, prescription details, clinical events, outpatient

laboratory test results, preventive care, specialist referrals, hospital admissions, and major outcomes, including death. Data validation with original records (eg, specialist letters) is also available, although response rates since the pandemic period have been extremely low. CPRD has 2 primary care components: CPRD GOLD (practices that use Vision software) and CPRD Aurum (practices that use EMIS software). CPRD Aurum is expanding and can be linked to several additional data banks; the MAH will use it for the present PASS.

The CPRD Aurum data set comprises 99% English practices (https://cprd.com/Data). Most of the data are coded using SNOMED CT codes. As of March 2022, CPRD Aurum contained data on 13,400,000 current acceptable patients (i.e., active patients available for research) and 41,000,000 patients, including deceased and transferred-out patients.[48] Data include demographics, all general practitioner/healthcare professional consultations (eg, phone calls, letters, emails, in surgery, at home), diagnoses and symptoms, laboratory test results, treatments (including all prescriptions), all data referrals to other care providers, hospital discharge summary (date and codes), hospital clinic summary, preventive treatment and immunisations, and death (date and cause). The Hospital Episode Statistics (HES) database contains details of all admissions to National Health Service (NHS) hospitals in England (Accident & Emergency, Admitted Patient Care, Outpatients). CPRD Aurum records are linked to HES using a combination of the patient's NHS number, sex, and date of birth. Additional linked data sets include Death Registration data from the Office for National Statistics (ONS), which includes information on the official date and causes of death (using ICD codes), Mother-Baby Link, and an algorithm-based Pregnancy Register. The Mother-Baby Link and the Pregnancy Register are currently implemented only in CPRD GOLD; for patients in CPRD Aurum, the Mother-Baby Link and Pregnancy Register are not available, but information on pregnancy status and pregnancy outcomes is available as events reported by the general practitioner in the primary care medical records. Other COVID-19–related data sets could be explored.

Study applications need to be submitted to and approved by the CPRD Research Data Governance. RTI Health Solutions also needs to complete an institutional review board (IRB) application for non-human research status determination.

9.4.4. Additional exploration of data sources

9.4.4.1. Italy: AIFA National Italian Patient Registry, PASS-DUS (exploratory)

Paxlovid users in Italy are being registered in a national registry mandated by AIFA. More details about the AIFA registry for patients receiving COVID-19 oral antiviral agents and its data collection form is provided in Annex 4. The form covers information to be collected at enrolment and 1 section that needs to be completed via telephone follow-up 1 month later. The baseline form collects demographic and comorbidity information appropriate to identify the patients of interest for the PASS-DUS, including specific questions on pregnancy and renal and hepatic impairment.

AIFA issues periodic reports on use of COVID-19 oral antiviral treatments in aggregated form (i.e., no individual-level data are available); these reports are publicly available.[49] As of

04 May 2022 (10th report), 12,424 Paxlovid treatment courses had been administered in Italy, as well as 24,779 molnupiravir treatment courses. Therefore, the information in this patient registry is of great interest to the Paxlovid PASS.

Typically, after a new AIFA patient registry becomes available to prescribers, the corresponding MAH has access to a weekly report with the number of new prescriptions and of closed treatments. According to a new (pending to finalise) agreement between the Italian pharmaceutical companies' association and AIFA, the new reports available to companies will have more information, always in aggregated form. In the context of regulatory activities such as a PASS or post-authorisation efficacy study, some limited flexibility for the customisation of the reports exits. However, in the context of an emergency use approval, the current situation, only the public reports are available to the Paxlovid MAH.

We continue to monitor the situation via communications with the Paxlovid MAH affiliate in Italy, who has established communications with the AIFA registry contacts who have confirmed that at this stage, the AIFA registry cannot participate in the Paxlovid PASS since the new agreement between the Italian pharmaceutical association and AIFA is estimated to be executed toward the end of 2022. The plan is to reach out to AIFA early in 2023 to explore whether at that time the information collected in the patient registry could be leveraged for the Paxlovid PASS. In the meantime, we will use the information available in publicly available reports.

Linkages of the Italian national registry to regional or local health unit data sources are not expected at this time.

Originally Paxlovid could only be prescribed and dispensed in selected centres in each Italian region (described as *modality 1* in Section 9.4.4.1). As of April 2022, Paxlovid can be dispensed in pharmacies with a prescription also by general practitioners (described as *modality 2* in Section 9.4.4.1). The counts, but not the clinical characteristics of these patients are captured in the AIFA registry (D Striano, Pfizer Italy, email communication, 13 May 2022).

9.4.4.2. Italy: Regional and local health unit data sources (exploratory)

The Italian National Healthcare System is organised at the regional level: the national government sets standards for assistance and tax-based funding for each region, which regional governments are responsible for providing to all their inhabitants.

Italian regional and local health unit data sources have played a strong role in PASS, in particular for medications dispensed in community pharmacies reimbursed by the regions, but it is unclear at this point whether Paxlovid will be captured in these data sources. The national codes associated with market authorisation exist, but currently, per national regulations, general practitioners will only be able to identify eligible patients and refer them to one of the regional centres that will prescribe and dispense Paxlovid. These centres are

hospitals or hospital-like facilities. Pathways to identify eligible patients and facilitate access to Paxlovid are determined by each region.

We monitor the capture of Paxlovid prescriptions via data sources from regional and local health units via the Regional Health Agency of Tuscany (ARS Toscana) and the province of Caserta in Campania.

- Tuscany is an Italian region, with approximately 3.6 million inhabitants. The Regional Health Agency of Tuscany (ARS Toscana) is a research institute in the Tuscany region. The ARS Toscana data source comprises all information collected by the Tuscany region to account for the healthcare delivered to its inhabitants. Moreover, ARS Toscana collects data from regional initiatives. All data in the ARS Toscana data source can be linked at the individual level through a pseudoanonymous identifier. The ARS Toscana database routinely collects primary care and secondary care drug prescriptions for outpatient use and is able to link them at the individual level with hospital admissions, emergency care admissions, records of exemptions from copayment, diagnostic tests and procedures, causes of death, the mental health services register, the birth register, the spontaneous abortion register, and the induced terminations register. A pathology register is available, mostly recorded in free text, but with morphology and topographic SNOMED CT codes. Mother-child linkage is possible through the birth register.

- Similar information is available for the province of Caserta, in Campania, with approximately 1 million inhabitants.

9.4.4.3. United Kingdom: OpenSAFELY (exploratory)

OpenSAFELY[50,51] is a secure platform for analysis of electronic health data records in England stemming from a collaboration between the University of Oxford, the London School of Hygiene and Tropical Medicine, the TPP and EMIS suppliers of electronic health records, and NHS England. NHS England handles information governance and permissions. The collaboration was developed to support urgent research in the context of the COVID-19 emergency. Data are maintained within the secure environments of the servers where they reside and are not allowed to move from their original location. In addition, researchers cannot manipulate raw data; instead, they must use the OpenSAFELY tools and information technology (IT) systems to write their analysis code and then run it against dummy data provided by OpenSAFELY. When the code is ready, it is executed by OpenSAFELY; researchers view the study results, tables, and graphs.

OpenSAFELY has strict open-source and transparency policies. The open-source policy limits the software and IT systems that can be used for the analysis. Currently the platform supports only statistical analysis code written with Stata, R, or Python; it requires that researchers use and are knowledgeable of the Git and GitHub IT systems. Those systems are aligned with best practices regarding task management and code review. The transparency

policy determines that all analysis code executed in the platform is shared for review and re-use by other investigators using the platform.

OpenSAFELY includes data on around 24 million individuals whose general practitioners use the TPP SystmOne primary care clinical information system (44% of the English population). The collaboration is also currently developing support for the practices using the EMIS system, which would bring the patient population covered to a total of 58 million people in England.

The reason for proposing to use OpenSAFELY is that it complements the proposed CPRD Aurum, and its use would largely increase the size of the study population. OpenSAFELY has access to the same linkages as CPRD Aurum plus access to outpatient hospital appointments and in-hospital treatments for COVID-19. Another important advantage of OpenSAFELY is that the lag times are shorter than in CPRD Aurum; eg, the lag for HES linkages with OpenSAFELY is 1 to 2 months compared with 11 months with CPRD Aurum. A caveat is that the research team has no previous experience using this data source, and the OpenSAFELY support team does not act as a data research partner for its data. Therefore, the research team is exploring how to integrate OpenSAFELY into the present PASS.

Table 7 describes the main features of OpenSAFELY and CPRD Aurum.

Table 7. Main features of OpenSAFELY and CPRD Aurum

Feature	OpenSAFELY	CPRD Aurum
UK population[a]	66,647,112	66,647,112
Database population	24 million (100% in England)	13 million (99% in England)
Electronic healthcare system	TPP SystmOne (40% of English population) EMIS (under development)	EMIS (56% of English population)
Database type	Primary healthcare electronic medical record database plus complete linkage to HES and other data	Primary healthcare electronic medical record database plus high-coverage linkage to HES and other data
Linked data sets	• Hospital Admissions • Intensive care admissions (COVID-19 only) • Emergency attendances • Death registry • COVID-19 test results • Deprivation data • In-hospital deaths (COVID-19 only) • In-hospital treatments for COVID-19 • Outpatient hospital appointments	• Hospital admissions (including COVID-19) • Intensive care admissions (COVID-19) • Emergency attendances • Death registry • COVID-19 test results • Deprivation data/socioeconomic measures • Cancer registry and treatment • Mental health services • Mother-Baby Link and Pregnancy Register algorithms (currently only in CPRD GOLD; in development in CPRD Aurum)
Drug dictionary codes/ therapeutic classification	dm+d	dm+d and Gemscript

Table 7. Main features of OpenSAFELY and CPRD Aurum

Feature	OpenSAFELY	CPRD Aurum
Disease and procedure coding system(s)	CTV3 Read codes and, for EMIS, SNOMED CT and local EMIS® codes; ICD-10 for HES linkages	SNOMED CT and local EMIS® codes; ICD-10 for HES linkages
Lag time linkages for HES	1-2 month	Currently at least 11 months
Access	• Only approved users • Project approval required from NHS England	• Through paid CPRD licence • Subject to protocol approval via CPRD's Research Data Governance Process
In-hospital treatments for COVID-19	Yes	No (plan to reach out to explore whether these linkages would be possible)
Laboratory test results	Yes, from primary care health records	Yes, from primary care health records
Data Security	OpenSAFELY does not allow moving patient data outside the secure environments where they already reside. Data reside centrally, and analysis programmes also run centrally. Analysis programmes are written by researchers.	Data are downloaded locally, and researchers have access to pseudonymised patient data in electronic repositories protected by each institution under the requirements of a licence and/or data use agreement with CPRD.
Can analytical files be downloaded locally?	No, only dummy data sets that can support the programming of analytical code	Yes
Software required to run analysis	Stata, R, or Python	Any
Knowledge and implementation of other IT systems required?	Git/GitHub	None
Open access policy	• All platform activity is publicly logged. All code for data management and analysis is shared centrally, under open licences and by default, for scientific review and efficient re-use.	All scripts and codes lists are kept by the investigators running the different studies according to their institution's policies.
Transparency	• All projects started within OpenSAFELY are visible to the public. • OpenSAFELY requires all researchers to archive and publish their analytic code, changes are shared publicly.	• A list of approved projects using CPRD data is publicly available from CPRD´s site (https://cprd.com/approved-studies-using-cprd-data). • A list of publications using CPRD data is publicly available from CPRD's site (https://cprd.com/bibliography)

a. UK population as of 01 January 2019 (estimated; this is the last available estimate).[52]

9.5. Study size

In this study, the duration of the observation period is bound by the dates for producing regulatory reports. For the safety component, all individuals meeting the study´s eligibility criteria during the study period will be included.

The number of treatments prescribed in various countries is presented in Section 9.4. Numbers by exposure group in each data source will be obtained in interim analyses.

The size of the exposed pregnant population is anticipated to be very small, given the strong recommendation against using Paxlovid during pregnancy or becoming pregnant during treatment with Paxlovid in the EU and UK SmPCs (Section 7). All other EMA-approved drugs to treat COVID-19 are also not recommended for use in pregnancy (Sections 9.1.1 and 9.1.2). It is likely that only relatively common outcomes will be observed with some certainty, given that the anticipated size of the study population is small.

For orientation regarding the study size, information from 2 data sources is provided. OpenSAFELY[17] reports that, of 115,190 individuals aged 12 years old or older who were eligible for COVID-19 treatment from 11 December 2021 through 23 February 2022, 56.2% were women and 31.6% were aged 12 to 49 years old. If the distribution of sex were the same across age categories, one could expect 115,190 × 0.562 × 0.316 = 20,432 eligible women aged 12 to 49 years (numbers of individuals are rounded down to nearest smaller integer). Extending these assumptions to treated individuals, 1,422 women 12 to 49 years old would have been treated with Paxlovid and 965 with molnupiravir. Pregnancy rates have been reported as 10.3% in women aged 15 to 44 years in the US in 2005;[53] assuming that this number can be applied as a percentage to the previously mentioned subtotals, one might estimate that, in OpenSAFELY from mid-December 2021 to mid-February 2022, 2104 eligible women were pregnant, of whom 146 were treated with Paxlovid and 99 were treated with molnupiravir. These numbers are likely overestimates because the age categories reported by OpenSAFELY include teenage and perimenopausal women (who would have a lower pregnancy rate than the source population for referenced pregnancy rate) and, more importantly, because the SmPCs for Paxlovid and molnupiravir recommend against use in pregnancy.

In SNDS, 12,179 individuals 16 years old or older used Paxlovid between 4 February and 29 June 2022; use increased each month.[42] Of these individuals, 1256 were women aged younger than 50 years. Following the same logic, calculations result in 125 pregnant women treated with Paxlovid; again, this is likely an overestimate, especially knowing that the mean age at Paxlovid use among individuals (of any sex) younger than 50 years of age was 38.8 years. Furthermore, 22% of Paxlovid users younger than 50 years old did not have documented COVID-19 tests in the 10 days before or after receiving Paxlovid.

Table 8 contains precision estimates for proportions of Paxlovid-exposed women that we might observe for the target population. The numbers of patients represent numbers of

Paxlovid users that we might observe in the study. For example, if the study identifies 10,000 Paxlovid users and 5% are pregnant, the 95% confidence interval (CI) will be (4.6%-5.4%).

Table 8. Precision (95% confidence intervals) expected for proportions of Paxlovid users in the target population

Number of patients	Potentially observed percentage of Paxlovid users in the target population					
	1%	5%	10%	20%	30%	40%
1000	(0.5-1.8)	(3.7-6.5)	(8.2-12.0)	(17.6-22.6)	(27.2-32.9)	(36.9-43.1)
2000	(0.6-1.5)	(4.1-6.0)	(8.7-11.4)	(18.3-21.8)	(28.0-32.1)	(37.8-42.2)
3000	(0.7-1.4)	(4.2-5.8)	(8.9-11.1)	(18.6-21.5)	(28.4-31.7)	(38.2-41.8)
4000	(0.7-1.4)	(4.3-5.7)	(9.1-11.0)	(18.8-21.3)	(28.6-31.4)	(38.5-41.5)
5000	(0.7-1.3)	(4.4-5.6)	(9.2-10.9)	(18.9-21.1)	(28.7-31.3)	(38.6-41.4)
10,000	(0.8-1.2)	(4.6-5.4)	(9.4-10.6)	(19.2-20.8)	(29.1-30.9)	(39.0-41.0)

Note: Confidence intervals were calculated using the Clopper-Pearson method for the binomial distribution.[54]

Table 9 provides some precision estimates that can be anticipated for comparative analyses for various study sizes that may be observed in the present study, for reference. Calculations for this table assumed that the true relative risk is 1 and that study population will have 3 unexposed pregnant women in the comparison group for each Paxlovid-exposed pregnant woman; this is based on the comparison with unexposed women. For example, if the study size were 280 Paxlovid-exposed pregnant women and 840 unexposed pregnant women, comparative analyses might result in a risk ratio 95% CI whose upper limit is under 3.0 with 0.8 probability for major congenital malformations.

Table 9. Study sizes needed for the upper limit of the risk ratio 95% confidence intervals to be below selected thresholds with a probability of 0.8 among pregnant women

Outcome	Assumed prevalence	Upper limit of 95% confidence interval	Exposed:Unexposed pregnant women
Small for gestational age	10%[a]	5	37:111
		4	50:150
		3	80:240
		2.5	115:345
		2	200:600
Major congenital malformations	3%[55]	5	130:390
		4	177:531
		3	280:840
		2.5	405:1,215
		2	705:2,115
Stillbirth	0.6%[56]	11	300:900
		8	400:1,200
		5	675:2,025

Table 9. Study sizes needed for the upper limit of the risk ratio 95% confidence intervals to be below selected thresholds with a probability of 0.8 among pregnant women

Outcome	Assumed prevalence	Upper limit of 95% confidence interval	Exposed:Unexposed pregnant women
		3	1,440:4,320
		2.5	2,065:6,195
		2	3,610:10,830

Note: Outcomes are listed in order of decreasing prevalence. Assumptions underlying these calculations:
- No difference in risk between the exposed and unexposed (i.e., risk ratio = 1).
- Ratio of exposed to unexposed was 1:3.
- Probability that the upper limit of 95% CI will be as stated = 0.8.
- Calculations were done using the "Study Size" tool in Episheet [57]

a. Assumed prevalence of 10% based on definition of birth weight below 10th percentile for gestational age.

9.6. Data management

This study will be conducted in a distributed manner, using a common protocol, CDM, and common analytics programmes based on existing health data, as far as possible. We count on a hybrid approach, where some of the data access partners (DAPs) may be able to run a script that is provided and others may need to run analyses themselves. The following steps will be implemented when access to individual-level data is possible:

1. Extraction, transformation, and loading (ETL) of data to a CDM. To harmonise the structure of the data sets stored and maintained by each data partner, a shared syntactic foundation will be used. The CDM that will be used has been developed during the IMI-ConcePTION project.[58] In this CDM, data are represented in a common structure, but the contents of the data remain in their original format. The ETL design for each study is shared in a searchable Findability, Accessibility, Interoperability, and Re-use of digital assets (FAIR) catalogue. The Vaccine Monitoring Collaboration for Europe (VAC4EU) FAIR data catalogue is a metadata management tool designed to contain searchable metadata describing organisations that can provide access to specific data sources. Data quality checks will be conducted to measure the integrity of the ETL, as well as internal consistency within the context of the CDM (see Section 9.8).

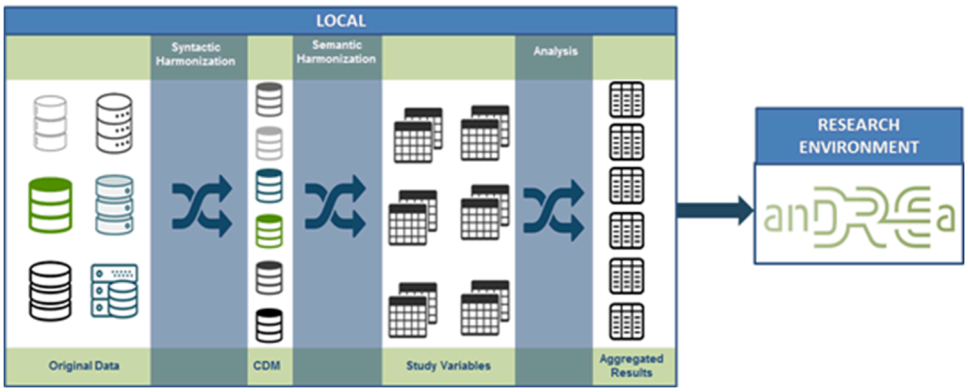
2. Second, to reconcile differences across diagnostic terminologies, a shared semantic foundation is built for the definition of events under study by collecting relevant concepts in a structured fashion using a standardised event definition template. This is conducted by mapping relevant disease concepts to ICD-10, ICD-9 (*International Statistical Classification of Diseases, Ninth Revision*), SNOMED CT, READ, or International Classification of Primary Care (ICPC) terminologies starting with a modified version of the ADVANCE Codemapper in VAC4EU.[59] Codes can be tagged as being specific (narrow) or possible (broader) allowing for variation of the

sensitivity of the event definition. Codes that are produced are reviewed by the DAPs and study team and listed in a study code lists using a VAC4EU R function, which subsequently gets incorporated in the R script for data transformation.

3. Third, following conversion to harmonised study variable sets, R and SAS scripts for the calculation of incidence and prevalence will be distributed to DAPs for local deployment. The aggregated results produced by these scripts will then be uploaded to the Digital Research Environment (DRE) for pooled analysis and visualisation (see Figure 2). The DRE, which is made available through the University Medical Center Utrecht (https://www.andrea-consortium.org/), is a cloud-based, globally available research environment where data are stored and organised securely and where researchers can collaborate (https://www.andrea-consortium.org/azure-dre/).

In case access to individual-level data is not possible, and only count/aggregated data can be used, we will provide the DAP with the shell tables that need to be filled and the exact definitions using a code book.

Figure 2. Data management plan



9.6.1. Record retention

Validation of the quality control of the statistical analysis will be documented by the coordinating centre. The final study protocol and amendments, the final statistical report, statistical programmes, aggregated results, and output files will be archived on a study-specific, secure central server.

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, DAPs will keep all study-related records, including analysis files, syntaxes, ETL specifications, output of data quality checks and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone call reports). The records will be retained by DAPs according to local regulations or as specified in the vendor contract, whichever is longer. DAPs must ensure that the records continue to be stored securely for so long as they are retained. It is the responsibility of the coordinating centre to inform the other investigators or institutions regarding when these documents no longer need to be retained.

For requests for access to data for audit purposes, only aggregated data from all DAPs will be available on the DRE. The audit trail will consist of a detailed description of the methods to extract and process the records from the data sources. Access to raw data at each data source research centre will require the data requestor to obtain a licence or apply for approval at a research committee and to fulfil the conditions required under the governance rules of each data source.

If the DRE environment becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless the coordinating centre and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years or as required by applicable local regulations.

The coordinating centre must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.6.2. Data extraction

Each DAP will create ETL specifications using the standard ConcePTION ETL design template for v2.2 (accessible via this link: https://docs.google.com/document/d/1SWi31tnNJL7u5jJLbBHmoZa7AvfcVaqX7jiXgL9uAWg/edit). Following completion of this template and review by the study team, each DAP will extract the relevant study data locally using its software (eg, Stata, SAS, R, Oracle). These data will be loaded into the ConcePTION CDM structure in csv (comma-separated value) format. These data remain local (see Figure 2).

9.6.3. Data processing and transformation

Data processing and transformation will be conducted using R (and SAS quality-control code) against the syntactically harmonised CDM. The scripts will first transform the data in the syntactically harmonised CDM to semantically harmonised study variables (see Figure 2). Following creation of study variables, the data will be characterised. This characterisation will include calculation of code counts and incidence rates, as well as benchmarking within the data source (over time), between data sources, and externally (against published estimates). Subsequently, code to conduct analysis against semantically harmonised study variables will be distributed and run locally to produce aggregated results. The scripts for these processing and analysis steps will be developed and tested centrally and sent to the DAPs.

The scripts will be structured in modular form to ensure transparency. Functions to be used in the modules will be either standard packages or packages specifically designed, developed, and tested for multidatabase studies. Scripts may be double-coded in SAS and R, and quality checks will be thoroughly documented.

The DAPs will run the code locally and send aggregated analysis results to the DRE using a secure file transfer protocol. In the DRE, results will be further plotted, inspected (for quality assessment), and pooled (if needed) for final reporting.

All final statistical computations will be performed on the DRE using R. For the quality-control scripts, SAS (SAS Institute; Cary, North Carolina) will be used. DAPs will have access to the workspace for script verification.

Aggregated results, ETL specifications, and a repository of study scripts will be stored in the DRE.

9.6.4. Data access

Within the DRE, each project-specific area consists of a separate secure folder called a "workspace." Each workspace is secured behind a firewall. Each workspace can be accessed only by users specific to its respective data source. Access to this workspace is possible only with double authentication using an identification code and password together with the user's mobile phone for authentication. Upload of files is possible for all researchers with access to the workspace within the DRE. The DRE offers tools to control and monitor which activities take place within projects, in compliance with General Data Protection Regulations and Good Clinical Research Practices.

Download of files is possible only after requesting and receiving permission from a workspace member with an "owner" role. Owner roles will be assigned to the project principal investigators, who will be responsible for managing download requests and verification of the privacy aspects.

9.6.5. Data quality checks

For all data sources that will use the ConcePTION CDM and a common R script, the data quality will be verified using 3 different checks (Sections 9.6.5.1 through 9.6.5.3).

9.6.5.1. Level 1 quality checks (completeness of ETL)

Level 1 data checks review the completeness and content of each variable in each table of the CDM to ensure that the required variables contain data and conform to the formats specified by the CDM specifications (eg, data types, variable lengths, formats, acceptable values). Level 1 checks of R code and instructions are independent of any study and publicly available on the IMI-ConcePTION GitHub (https://github.com/IMI-ConcePTION/Level-1-checks). They should be run on each new data instance that undergoes ETL.

Specific objectives of level 1 checks:

- To assess the integrity of the ETL process from the original data to the ConcePTION CDM for each DAP

- To provide feedback on the integrity of the ETL to the DAP iteratively for the refinement of the DAP's ETL procedure

- To produce high-level characterisation of the data that has undergone ETL to the instance of the CDM in terms of presence/absence of CDM tables and columns, missingness in key variables, frequencies of categorical variables, and distribution of dates and continuous variables

The level 1 checks are divided in 5 major steps:

Step 1: Check ConcePTION CDM table formatting

1. Check if all rows of the CDM csv files in the working directory contain the correct number of variables.
2. Check if all variables in the CDM table are present irrespective of their content.
3. Check if variable names in the csv are written in lowercase.
4. Check for presence of all mandatory variables according to the ConcePTION CDM.
5. Check for presence of non-mandatory variables by comparing between the table of interest and the information recorded in the METADATA table.
6. Check presence of vocabularies for specific variables.
7. Assess formats for all values and compare with a list of acceptable formats that has been filled out in the METADATA table.

Step 2: Conduct missing data analysis

1. Tabulate missingness in all variables, overall and by calendar year (in the tables that contain a date variable).
2. Stratify missing data by meaning (in the tables that contain a meaning variable).
3. Display missing data using bar charts for each CDM table and report as counts and percentages.
4. Stratify missing data by meaning or calendar year, display using line charts for each CDM table, and report as counts and percentages.
5. Stratify missing data by meaning and calendar year, display using heat maps for each CDM table, and report as counts and percentages.

Step 3: Check dates

1. Check if dates are in the correct format (8 characters).
2. Check if date variables contain allowable values, for example:
    - Year: 1995 to present (exception for dates that represent end of follow-up where years in the future will be allowed)
    - Month: 01-12
    - Day: 01-31

Step 4: Check conventions and construct frequency tables of other and categorical variables.

1. Check if the table of interest contains any duplicate rows.
2. Check that all conventions for the table of interest have been adhered to.
3. Construct frequency tables of categorical variables, overall and by calendar year (when the table of interest contains a date variable).
4. Stratify all frequency tables by meaning when the table of interest contains a meaning variable.
5. Report results separately for variables with 2 or more categories.
6. Display the results graphically with bar charts or line charts.

Step 5: Check distribution of continuous variables and date variables

1. Report mean, median, interquartile range, skewness and kurtosis for continuous variables.
2. Report distribution of date variables as counts of dates overall and by calendar year.
3. Stratify all results by the meaning variable if the table of interest contains one.
4. Display results graphically with bar charts or line charts.

Level 1 R scripts output an R Markdown report that is submitted to the DRE and is inspected and assessed by the study team and the DAP, according to a structured template format.

9.6.5.2. Level 2 quality checks (internal consistency of data in CDM)

Aims of level 2 quality checks are to assess internal consistency of the data both within and between tables of the ConcePTION CDM instance for each DAP. The R code for level 2 checks is independent of any study and publicly available on the IMI-ConcePTION GitHub (https://github.com/IMI-ConcePTION/Level-2-checks).

Level 2 data checks assess the logical relationship and integrity of data values within a variable or between 2 or more variables within and between tables. Examples of this type of check include observations occurring before a birth date, observations occurring after a recorded death date, a parent aged 12 years or younger, etc.

The level 2 checks are divided into 8 major steps:

- Detect event dates that occur before birth date.
- Detect event dates after date of death.
- Detect event dates outside observation periods.
- Detect subjects included in a CDM table without a corresponding record in the PERSONS table.

- Detect observations associated with a visit_occurrence_id that occurs before the visit_start_date.
- Detect observations associated with a visit_occurrence_id that occurs after the visit_end_date.
- Detect observations associated with a visit_occurrence_id for which the associated person_id differs from that in the VISIT_OCCURRENCE table.
- Detect subjects indicated in PERSON_RELATIONSHIPS as the parent of a child with a birth_date less than 12 years prior to the recorded birth_date of the associated child.

Level 2 check scripts output an R Markdown report that is submitted to the DRE and is inspected and assessed by the study team and the DAP, according to a structured template format.

9.6.5.3. Level 3 quality checks (study variable check)

Level 3 checks focus on key study variables (population, medications, diagnoses, pregnancy algorithm, medical observations, survey observations and vaccines, lifestyle) based on time anchoring of the population, exclusion criteria and semantic harmonisation of outcomes, exposures, and covariates and are divided into different modules that may be included or not depending on the study questions. Level 3 checks allow for benchmarking within a data source over time, between data sources, and with external benchmark data. Level 3 checks are in development to optimise detection of deviations.

9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.7.1. Descriptive analyses

Description of the baseline characteristics for the exposed (Paxlovid) and comparator cohorts will be reported as means, standard deviations, medians, and other quartiles for continuous variables and as counts and proportions for categorical variables. The missingness of variables will also be described.

To describe the relative imbalance of characteristics between Paxlovid-exposed and comparator groups, absolute standardised differences will be calculated for each baseline characteristic. For categorical variables with more than 2 levels, we will calculate an overall standardised difference across all levels.

For pregnancy and offspring outcomes, prevalence and 95% CIs will be reported at the end of follow-up.

9.7.2. Unadjusted outcome measures

In the population of pregnant women, unadjusted prevalence, prevalence ratio, and prevalence difference for each pregnancy, offspring, and maternal outcome among Paxlovid users versus each of the 2 comparator groups separately (with active comparator molnupiravir where available), will be estimated, along with their 95% CIs. Subgroup analyses will be conducted by subgroups defined by demographic and clinical characteristics, as well as other covariates of interest, if the target population sizes are adequate.

For major congenital malformations, the live birth and total prevalences per the EUROCAT definition will be calculated.[60]

Risk/prevalence ratios will be calculated only if at least 5 outcomes are present among the individuals that will be included in a given analysis in the study population from a given data source.

9.7.3. Adjustment for baseline imbalances

Individuals in each cohort under study may have different characteristics that may influence their exposure and their risk of outcomes. To account for such potential confounding, we will stratify by COVID-19 severity (of note, per the indication, patients should have mild COVID-19 at treatment start) and estimate the adjusted risk/prevalence ratios and 95% CIs.

For adjustment, taking into consideration that some of the study outcomes will be rare, while exposure will likely be more evenly distributed, propensity score methods are planned, such as inverse probability of treatment weighting. Propensity score matching with matching ratio up to 1 Paxlovid-exposed individual to 5 individuals in either comparison group will also be considered.

Risk/prevalence ratios will be calculated only if at least 5 outcomes are present among the individuals that will be included in a given outcome analysis in the study population from a given data source.

More details, including how correlated observations such as offspring from the same mother will be treated, will be provided in the SAP.

9.7.3.1. Sensitivity analyses

Sensitivity analyses will include

1. A modification of the outcome definition (Section 9.3.2) such that completed pregnancies with unknown outcome will also be incorporated.

2. A modification of the study period (Section 9.9) to ensure that short pregnancies that start late in the study observation period are not selectively incorporated into the study population; this analysis will stop the accrual of pregnancies earlier to allow at least 10 months of data between LMP and the last observed data point.

9.7.3.2. Meta-analysis

Analyses will be conducted separately within each data source. Using the main estimates from each data source, appropriate random-effects meta-analytic methods will be used to obtain a combined effect estimate. The heterogeneity across data sources will be checked, and a forest plot will be produced with the data sources and the pooled estimate.

Outcomes for meta-analysis will include all outcomes listed. A minimum of 3 data points will be required (i.e., results from at least 3 data sources need to be available to proceed with meta-analysis for a given outcome). Risk ratios obtained from sensitivity analyses may be meta-analysed if numbers are adequate.

9.7.4. Small cell count policy

The small cell count rules specified in Table 10 will be taken into account when presenting results of the study. The cover page, statistical analysis, and results section of study reports will contain the following boxed statement*:

> This report is for regulatory communications only. For any dissemination beyond regulatory authorities, please refer to the data protection rules, and apply the masking rules regarding small cell count restrictions in Section 9.7 and Table 10.

Table 10. Small cell count rules for reporting results

	SNDS (France)	SIDIAP (Catalonia, Spain)	CPRD Aurum (UK)
Numbers to be masked	1-10	1-4	1-4
Text to be used in redactions	≤ 10	< 5	< 5
Possible to share with SIGMA Paxlovid PASS research centres	No	Yes	Yes
Possible to share with regulatory authorities. Note: report is provided to authorities by MAH (Pfizer)	No	Yes	Yes
Comments		Not applicable	A clear statement about cell count suppression is required

* Note: The boxed text will be included in study reports; the section number and table refer to the report.

9.8. Quality control

All key study documents, such as the analysis plan and study reports, will undergo quality-control review, senior scientific review, and editorial review. At the SIGMA coordinating centre, an independent Office of Quality Assurance can perform audits and assessments that involve various aspects of projects, including education and training documentation, data entry and data-transfer procedures and documentation, and IRB documentation. Such audits are conducted by the centre's Office of Quality Assurance according to established criteria in standard operating procedures and other applicable procedures.

Again, according to the procedures developed in the IMI-ConcePTION project, level 1 data checks review the completeness and content of each variable in each table of the CDM to ensure that the required variables contain data and conform to the formats specified by the CDM specifications (eg, data types, variable lengths, formats, acceptable values). Level 2 data checks assess the logical relationship and integrity of data values within a variable or between 2 or more variables within and between tables. Level 3 data checks produce incidence and prevalence rates or proportions and trends over time within a data source (by examining output by age and year) for benchmarking between data sources and against external sources. For details, refer to descriptions of the data quality checks in Section 9.6.5.

9.9. Limitations of the research methods

Key limitations of this study, as foreseen at this time, are listed below.

- *Identifying exposure* is a key uncertainty at the time of preparation of this document. In some data sources, Paxlovid distribution is using the channels that trigger a record in routinely available electronic health records or healthcare claims. This criterion was used to select the data sources listed in Section 9.4. However, in other countries, if Paxlovid is mostly distributed from hospital pharmacies, as has happened in Italy in the first months of Paxlovid availability, data sources commonly used for pharmacoepidemiologic research will not be able to access this information; in Italy, this information is available, in aggregated form, from AIFA. If Paxlovid distribution is documented only in a specific registry, linkage to this registry would be needed for the present study. The MAH and the research team are in close communication sharing information about country-specific distribution channels and sales volume as the information becomes available. The same consideration applies to the comparator drug molnupiravir, which appears to use the same distribution channels as Paxlovid in some data sources.

- *Identifying COVID-19 episodes*. Currently, in many countries, individuals can self-test for COVID-19 at home. As a result, positive test results in the outpatient setting may not be documented in the individual's health records. Furthermore, the intensity of screening has decreased. Documented COVID-19 is an inclusion criterion for this study for all exposure groups; individuals with COVID-19 whose diagnosis or positive test result is not documented will not be identified as eligible for inclusion in this study. For reference, in data from the SNDS in France, 27% of Paxlovid users did

not have documented COVID-19 tests in the 10 days before or after Paxlovid use.[42] Pregnant individuals who test positive on a screening test at the time of hospitalisation for delivery will not be eligible for the study because they do not contribute person-time to the study.

- *Ascertaining COVID-19 vaccination status* if Paxlovid use can be captured only in data sources that do not capture vaccination. Paxlovid is indicated for individuals who are at increased risk for progression to severe COVID-19, and unvaccinated individuals can be considered as being at increased risk for progression to severe COVID-19; this will depend on the country-specific use recommendations. If the available data sources do not capture vaccination, any potentially increased risk for progression to severe COVID-19 due to lack of vaccination will not be captured. At this time, the 3 proposed data sources capture COVID-19 vaccination.

- *Size of target populations*. The target population includes individuals who should not receive Paxlovid per the SmPCs. For this reason, it is expected that the number of Paxlovid-exposed individuals in the target population will be small. If the number of individuals is too small to sustain comparative analyses (please see Section 9.7), analyses will be descriptive only.

- *Comparator group*. At the time of preparing this document, no treatments specific to COVID-19 with an approved indication and mode of use similar to Paxlovid are authorised in the EU. As described in Section 9.1.1, molnupiravir has not been authorised in the EU, but the EMA supports national authorities that may want to decide on its early use[12]; for example, AIFA has recently authorised its use in Italy,[13] and use has been documented. Molnupiravir is a reasonable active comparator and has been selected to serve as such. As noted, molnupiravir appears to use the same distribution channels as Paxlovid, at least in some data sources. Because molnupiravir was not used or not captured in some of the selected data sources (SIDIAP, SNDS) at the time of preparing this protocol, an alternative comparison group is included: unexposed individuals who were at increased risk for progression to severe COVID-19.

- *Channelling and potential for residual confounding.* Using an active comparator with a similar indication mitigates confounding by design. Channelling will be addressed analytically (eg, propensity score weighting). It is anticipated that channelling would be more substantial when using an unexposed comparator group.

- *Pregnancies detected while they are still ongoing.* The date of pregnancy start may be unavailable in pregnancies that end before 20 gestational weeks. In such pregnancies, the start date of pregnancy could be imputed (for example, using predictive models based on pregnancies with observed start date). Some pregnancies identified as ongoing (because they lack information on pregnancy end) cannot plausibly be still ongoing, possibly reflecting that the end of pregnancy was not captured in the data

source. In data sources with a well-established birth registry or other reliable sources of information, pregnancies without information on pregnancy end might be assumed to represent foetal losses. Sensitivity analyses will assume that some pregnancies with unknown outcomes are spontaneous abortions. Additionally, to ensure that short pregnancies that start late in the study observation period are not selectively incorporated in the study population (inflating the observed prevalence of spontaneous abortions and preterm deliveries), a sensitivity analysis will stop the accrual of pregnancies starting at some point in 2024 (date to be determined), allowing at least 10 months of data before the last observed data point.

- *Simultaneous use of medications that are contraindicated or can have substantial interactions with Paxlovid*. This PASS will be able to find prescriptions or dispensings for these medications, but the data sources will not be able to capture whether patients stop taking the medications for a few days around the period of Paxlovid treatment.

- *Evolving uses of Paxlovid*. Paxlovid has a clearly defined indication in the EU and UK SmPCs; however, the press has disseminated various potential uses that are not in alignment with the SmPCs, such as longer treatment course if symptoms rebound after the 5-day course,[61] use as postexposure prophylaxis (noting that the clinical trial did not meet its prespecified endpoint),[62] as treatment for long COVID-19,[63,64] and paediatric use.[65]

- *Characterising the study population in relation to certain aspects of the indications for Paxlovid and molnupiravir.* Some aspects of the indications for Paxlovid and molnupiravir cannot be ascertained in data sources typically used for PASSs. Need for or use of supplemental oxygen will not be well captured in the data sources. Increased risk for progression to severe COVID-19 may involve subjective determinations from healthcare providers not necessarily based on elements contained in medical records or claims data sources. Exact time since symptom onset will not be known.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

This is a non-interventional study using secondary data collection and does not pose any risks for individuals. Each DAP will apply for an independent ethics committee (IEC) review according to local regulations. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information. Furthermore, the proposed study is a non-interventional study reusing healthcare data (secondary data collection). All data collected in the study will be deidentified with no breach of confidentiality with regard to personal identifiers or health information. Data protection and privacy regulations will be respected in collecting, forwarding, processing, and storing data from study participants.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional review board/independent ethics committee

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs or other relevant authorities. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigour, and follow generally accepted research practices described in the following paragraphs.

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[66] and has been designed in line with the *ENCePP Guide on Methodological Standards in Pharmacoepidemiology*[67] and the UK MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions.[68] The *ENCePP Checklist for Study Protocols*[69] has been completed for the protocol (see Annex 2).

The study is a PASS and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline *Pharmacovigilance Planning E2E*[70] and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies*[4] and with the 2012 EU pharmacovigilance legislation, adopted 19 June 2012.[71] The study will comply with the study reporting requirements specified in Module VIII Section VIII.B.6.3.1., "Progress Reports," and Section VIII.B.6.3.2., "Final Study Report" of the *Guideline of Good Pharmacovigilance Practices*._ENREF_4[4]

In alignment with EMA GVP Module VIII Section VIII.B.2., study registration, the study, and its protocol will be registered in the European Union Electronic Register of Post-

authorisation Studies (EU PAS Register)[72] prior to the start of data collection. At completion, the final report or its summary will be posted.

The SIGMA research team and study sponsor adhere to the general principles of transparency and independence in the *ENCePP Code of Conduct*.[73]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol, progress report, and interim and final study reports will be submitted to the EMA Pharmacovigilance Risk Assessment Committee (PRAC) as agreed on in the risk management plan and included in other regulatory communications as relevant.

Study reports will be prepared using a template following the Guideline on Good Pharmacovigilance Practices (GVP) Module VIII, Section B.4.3.[4] Reports will include a progress report with a description of project start-up and subsequent activities, the evolution of the identified challenges for this study, and the list of anticipated data sources (per an ongoing feasibility assessment on Paxlovid distribution channels in various countries); 2 annual interim reports with the number of Paxlovid-exposed individuals overall and in each exposure group and preliminary outcome counts; a final report; and, if applicable, a paediatric report 6 months after the end of data collection for the final report.

As noted in Section 10.4, in alignment with EMA GVP Module VIII Section VIII.B.2, the study and its protocol will be registered in the EU PAS Register[72] prior to the start of data collection. At completion, the final report or its summary will be posted.

Study results will be published following recommendations of the International Committee of Medical Journal Editors,[74] and communication in appropriate scientific venues (eg, International Conference on Pharmacoepidemiology & Therapeutic Risk Management [ICPE]) will be considered. In its *Guidelines for Good Pharmacoepidemiology Practices (GPP)*, the International Society for Pharmacoepidemiology (ISPE) contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance."[66] In alignment with EMA *GVP Module VIII: Post-Authorisation Safety Studies*,[4] Section VIII.B.5, and the *ENCePP Code of Conduct*,[75] the MAH and investigators will agree upon a publication policy allowing the members of the research team to

independently prepare publications based on the study results, irrespective of data ownership. The MAH will be entitled to view the results and interpretations included in the manuscript and provide comments before submission of the manuscript for publication. The MAH and research team are aware that the MAH should communicate to the regulatory agency(ies) the final manuscript of the article within 2 weeks after first acceptance for publication.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the responsible parties are aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes," the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Use and Safety of Paxlovid During Pregnancy

EU PAS Register® number: not registered yet **Study reference number (if applicable):** protocol number C4671037

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection*	☒	☐	☐	6
1.1.2 End of data collection†	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	4, 6
1.1.4 Interim report(s)	☒	☐	☐	4, 6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	4, 6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	Cover, 4, 7, 8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4, 9.1, 9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section number**
3.1 Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	4, 9.1, 9.2, 9.7
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	4, 9.1, 9.4
3.3 Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	4, 9.7

* Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

† Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section number**
3.4	Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	4, 9.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section number**
4.1	Is the source population described?	☒	☐	☐	9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	4, 9.2.2
	4.2.2 Age and sex	☒	☐	☐	4, 9.1, 9.2.1
	4.2.3 Country of origin	☐	☒	☐	
	4.2.4 Disease/indication	☒	☐	☐	4, 9.1, 9.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.1
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1, 9.5

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section number**
5.1	Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	4, 9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3	Is exposure categorised according to time windows?	☐	☒	☐	
5.4	Is intensity of exposure addressed? (eg, dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	4, 9.3.1

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	4, 9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3	Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQOL, QALYs, DALYs, healthcare services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section number**
7.1	Does the protocol address ways to measure confounding? (eg, confounding by indication)	☒	☐	☐	4, 9.7
7.2	Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	4, 9.1 9.2.1
7.3	Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.3.2

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section number**
8.1	Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3, 9.4, Annex 4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section number**
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3, 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3, 9.4, Annex 4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3, 9.4, Annex 4
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3, 9.4
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, comorbidity, comedications, lifestyle)	☒	☐	☐	9.3, 9.4, Annex 4
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3, 9.4, Annex 4
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3, 9.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3, 9.4, Annex 4
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	4, 9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	4, 9.7
10.4 Are stratified analyses included?	☒	☐	☐	4, 9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	4, 9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.6.5, 9.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.3.2, 9.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section number**
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6, 9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	3, 9.1, 9.4, Annex 4

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section number**
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	4, 6, 12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	4, 6, 12

Comments:

Main author of the protocol: Andrea Margulis	
Signature & date:	Andrea Margulis 10-Nov-2022

ANNEX 3. PERINATAL PHARMACOEPIDEMIOLOGY RESEARCH CHECKLIST

This checklist lists methods-related elements that are key in perinatal pharmacoepidemiology research. The columns for yes, no, or not applicable (N/A) reflect whether each element is specified in the present document. The column for section number reflects where in the document the element is specified (if applicable).

#	Element	Yes	No	N/A	Section number
Source of information on beginning and end of pregnancy					
1	Source of information for start of pregnancy (eg, electronic algorithm, ultrasound)	X			9.2.1
2	Source of information for pregnancy outcome date (eg, recorded codes for spontaneous abortion, date estimated using an algorithm)	X			9.2.1
Composition of the study population					
3	Multifetal pregnancies included in study population?	X			9.2.1
4	More than one pregnancy per woman included in study population?	X			9.2.1
5	Foetuses with chromosomal abnormalities included in study population?	X			9.2.1
6	Foetuses with major malformations included in study population?	X			9.2.1
7	Foetuses with minor malformations included in study population?	X			9.2.1
8	Non-live births included in denominator?	X			9.7
Mother-infant and father-infant linkages					
9	If mother-infant linkage was implemented, was the process described?	X			9.2.1 9.4
10	If mother-infant linkage was implemented, was the success rate reported?			X	
11	If mother-infant linkage was implemented, was the information taken from maternal vs. infant files?			X	
12	If father-infant linkage was implemented, was the process described?			X	
13	If father-infant linkage was implemented, was the success rate reported?			X	
Analytical aspects					
14	Unit of analysis for pregnancy outcomes		X		
15	Unit of analysis for foetal or infant outcomes		X		
16	Gestational age at start of follow-up		X		
17	Was intrafamily correlation considered?		X		
Comments: Mother-infant linkage was not yet implemented. The process has not been described in detail in this document. Father-infant linkage not needed in this study. Analytical aspects will be developed in the statistical analysis plan.					

N/A = not applicable.
Source: Margulis et al (76)

ANNEX 4. ADDITIONAL INFORMATION

Italian Medicines Agency (AIFA) registry for patients receiving COVID-19 oral antiviral agents, Italy

Based on the AIFA Determination published on O.J. n. 31 of 07 February 2022 (Paxlovid modality 1 in Section 9.4.4.1), selection of the patients who are eligible for treatment is entrusted to general practitioners and to any physicians in contact with the patient (including local home-caring units). Such physicians are only in charge of selecting and referring patients to a number of specified centres identified by the local administrative districts in each of the 20 regions. Prescription of the product is limited to the physicians working within these centres (any specialty) where the product can also be dispensed to the patient.

A registry monitoring form[77] should be completed for each patient, as per AIFA requirement. The eligibility criteria in the registry are the same for COVID-19 oral antiviral agents (Paxlovid and molnupiravir [Merck]). The patient needs to present with at least 1 of the following risk factors associated with possible progression to severe disease:

- Active oncologic/onco-haematologic disease
- Chronic kidney failure
- Severe bronchopneumopathy
- Primary or acquired immunodeficiency
- Obesity (body mass index ≥ 30)
- Severe cardiovascular disease (heart failure, coronary disease, cardiomyopathy)
- Decompensated diabetes mellitus

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